TAMPEREEN TEKNILLINEN YLIOPISTO
TAMPERE UNIVERSITY OF TECHNOLOGY

ALEKSI PAAKKUNAINEN

STUDIES ON DEOXYGENATION OF DECANE-1,2-DIOL DERIVATIVES WITH PINACOL-DERIVED CHLOROHYDROSILANE

Master of Science thesis

Examiners:
Adj. Prof. Nuno R. Candeias
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ABSTRACT

TAMPERE UNIVERSITY OF TECHNOLOGY
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In spite of the extensive studies, which have been carried out on the selective deoxygenation of secondary alcohols, it still poses a formidable challenge. The recent discovery of the reduction of salicylaldehydes with a system of a pinacol-derived chlorohydrosilane (PCS) and a Lewis base prompted the idea of adapting the procedure in the selective deoxygenation of vicinal diols. The most viable option of attaining such deoxygenations, after a thorough study of available literature, was to convert the hydroxyl groups to better leaving groups, to facilitate an intramolecular hydride delivery from PCS. Based on this hypothesis, the potential of PCS in the selective deoxygenation of decane-1,2-diol derivatives was investigated.

It was decided that the main focus of the project would be on the attempted deoxygenations of the secondary hydroxyl group of decane-1,2-diol, which required the syntheses of several secondary diol derivatives. The preparation of the secondary derivatives was carried out using a three-step pathway, where the primary hydroxyl group of the diol was first protected as a *tert*-butyldimethylsilyl (TBDMS) ether, after which the secondary hydroxyl group was functionalized. In the final step, the TBDMS-group was removed to restore the primary hydroxyl group.

The secondary hydroxyl group of decane-1,2-diol was successfully converted into tosylate and carbamate groups. The conversions of the secondary hydroxyl group into trichloroacetate and ethyl malonate moieties were also accomplished, although unintentional intramolecular transesterification during the deprotections resulted in the formation of mixtures of two regioisomers, which were used directly as starting materials in the deoxygenation stage due to isomer separation issues. Finally, the direct tosylation of the primary hydroxyl group was also performed with success, without the use of a protecting group.

The deoxygenations of the prepared intermediates were then attempted, using the combination of PCS and Lewis bases. Despite the various conducted experiments and the screening of a variety of Lewis bases for optimal catalytic activity, the deoxygenation of the synthetized decane-1,2-diol derivatives was not achieved. However, this work may serve as a reference point for future attempts of investigating other alternatives, where deoxygenations of this nature could be accomplished.

TIIVISTELMÄ

TAMPEREEN TEKNILLINEN YLIOPISTO
Teknis-luonnontieteellinen koulutusohjelma
ALEKSI PAAKKUNAINEN: Tutkimus dekaani-1,2-diolijohdannaisten deoksygenoimiseksi pinakoliperäisen kloorihydrosilaanin avulla
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Alkoholien selektiivinen deoksygenointi on edelleen haastavaa, vaikka aihetta on tutkittu kattavasti. Viime aikoina kehitettiin salisyylialdehydien pelkistysmenetelmä, jossa käytettiin pinakoliperäisen kloorihydrosilaanin (PCS) ja Lewis-emäksen yhdistelmää, ja johon perustuen pyrittiin johtamaan vastaava PCS-pelkistys visinaalisille dioleille. Kirjallisuuden arvioinnin jälkeen todettiin, että todennäköisin menetelmä kyseisten deoksygenointien saavuttamiseksi olisi muuttaa hydroksyyliryhmät paremmiksi lähteviksi ryhmiksi, jolloin PCS:n aiheuttama intramolekulaarinen hydridisiirtymä voisi toteutua. Tähän hypoteesiin nojaten päätettiin tutkia PCS:n potentiaalia dekaani-1,2-diolista valmistettujen johdannaisten deoksygenoinnissa.

Päätettiin, että projektin pääpainona oli dekaani-1,2-diolin sekundäärisen hydroksyyliryhmän deoksygenointi, mikä edellytti useiden sekundääristen diolijohdannaisten syntetisointia. Sekundääristen johdannaisten valmistuksessa käytettiin kolmivaiheista menetelmää, jossa ensimmäiseksi primäärinen hydroksyyliryhmä suojattiin *tert*–butyylidimetyylisilyylieetteriksi (TBDMS), jonka jälkeen sekundäärisen hydroksyyliryhmän avulla muodostettiin johdannainen. Viimeisessä vaiheessa TBDMS-ryhmä poistettiin ja primäärinen hydroksyyliryhmä muodostettiin uudelleen.

Sekundäärinen hydroksyyliryhmä muodostettiin onnistuneesti tosylaatiksi ja karbamaatiksi. Sekundäärisen hydroksyyliryhmän esteröinti trikloorisetaatiksi ja etyylimalonaatiksi toteutui myös, mutta suojaryhmän poiston aikana, ei-toivotun intramolekulaarisen transesteröinnin vaikutuksesta, tuotteeksi saatiin kahden regioisomeerin seos, jota käytettiin sellaisenaan lähtöaineena deoksygenointivaiheessa isomeerien erotukseen liittyvien ongelmien vuoksi. Lisäksi toteutettiin reaktio, jossa primäärinen hydroksyyliryhmä tosyloitiin ilman suojaryhmien käyttöä.

Valmistettujen välituotteiden deoksygenointitutkimukset suoritettiin PCS:n ja Lewis-emäksien yhdistelmää käyttäen. Useista erilaisista testeistä ja Lewis-emästen optimaalisen katalyyttisen aktiivisuuden seulonnasta huolimatta, syntetisoitujen dekaani-1,2-diolijohdannaisten deoksygenoitumista ei havaittu. Tästä huolimatta tämän projektin havainnot voivat toimia vertailukohtana tulevaisuudessa tehtäville vaihtoehtoisille tutkimuksille, joissa tämäntyyppisiä deoksygenointeja voitaisiin havaita.

PREFACE

This Master of Science thesis was written as a part of the Master's Degree Programme in Science and Engineering at Tampere University of Technology. The thesis work was carried out in the Laboratory of Chemistry and Bioengineering, between September 2017 and May 2018.

I am grateful to Adjunct Professor Nuno R. Candeias, for offering me this thesis project and acting as its examiner, and for the years of teaching and mentoring in the field of organic synthesis. I would also like to thank Master of Science Benedicta Assoah, for sharing her expertise during times of trouble, and for being the co-examiner to the thesis.

I am also grateful to the good people of the synthesis lab for their help and advice, and for building a friendly working environment filled with camaraderie and positivity. I thank friends and family for their support during my studies.

Finally, a very special recognition is extended to the folks of SA025, for all the years of good times and laughter.

In Tampere, Finland, on May 23rd, 2018

Aleksi Paakkunainen

Contents

LIST OF ABBREVIATIONS AND SYMBOLS

^{13}C	Carbon-13, Carbon atom isotope 13
^{19}F	Fluorine-19, Fluorine atom isotope 19
^{1}H	Proton
δ	Chemical shift (ppm) in NMR spectra
$CDCl_3$	Deuterated chloroform
d	Doublet, peak splitting pattern in NMR spectra
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-diisopropylethylamine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dd	Doublet of doublets, peak splitting pattern in NMR spectra
DMAP	4-dimethylaminopyridine
EDC·HCl	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
ESI	Electrospray ionization, technique in mass spectrometry
Et	Ethyl group
eq	Stoichiometric molar equivalent
HRMS	High resolution mass spectrometry
J	Coupling constant (Hz) in NMR spectra
LA	Lewis acid
LB	Lewis base
m	Multiplet, peak splitting pattern in NMR spectra
NMR	Nuclear magnetic resonance spectroscopy
PCS	Pinacol-derived chlorohydrosilane
Ph	Phenyl group
q	quartet, peak splitting pattern in NMR spectra
qd	quartet of doublets, peak splitting pattern in NMR spectra
r.t.	Room temperature
s	Singlet, peak pattern in NMR spectra
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethyl silyl group
TBDMSO	*tert*-butyldimethylsilyloxy group
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
Ts	Tosyl group, p-toluenesulfonyl group
t	triplet, peak splitting pattern in NMR spectra

1 Introduction

In the interest of manufacturing sustainable fossil-free products, such as fuels, polymers and chemicals, the processing of lignocellulosic biomass has been researched extensively over the past few years [1]. However, biomass-derived polyols are not usable as starting materials in most present-day industrial processes, due to their characteristic overfunctionalized oxygen-containing moieties [2]. Solubility issues, thermal instability and difficulties in derivatization have also been reported for polyols, which further emphasizes the need for the development of quick, efficient, versatile and cost-controlled deoxygenation methods [3].

The deoxygenations of alcohols have been researched for decades. In the 1970s, Barton and McCombie developed a procedure, where secondary alcohol derivatives were successfully deoxygenated with tri-*n*-butylstannane [4]. Although the Barton-McCombie deoxygenation is still renowned in the scientific community, alternatives have been searched, due to toxicity issues and a limited amount of suitable applications for the procedure [4] [5]. In recent years, the Lewis acid tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) has been identified as a catalyst in several reductive processes, where the reduction proceeds via hydrosilylation [6].

A novel method for the reduction of salicylaldehydes was recently reported by Assoah *et al.* [7]. In their procedure, a hydrosilyl ether obtained from the reaction of a salicylaldehyde and PCS in the presence of a Lewis base catalyst, underwent intramolecular hydride delivery at the carbonyl carbon to give the corresponding alcohol in high yield. Intriguing regio- and chemoselective properties were also observed for the PCS-procedure. In addition, Assoah *et al.* also presented a preliminary report on successfully using PCS in the reductive amination of salicylaldehyde, thus indicating the potential of PCS being a multifunctional reductive component.

Driven by the results obtained by Assoah *et al.*, a study on extending the observed reducing capabilities to terminal vicinal diol derivatives was conducted. The goal was to selectively reduce one of the hydroxyl groups, using a two-step pathway of functionalization and deoxygenation. For this purpose, decane-1,2-diol was chosen as starting material, from which six derivatives were prepared, so that one of the two hydroxyl groups was selectively functionalized. Each of the prepared substrates was subjected to various deoxygenation experiments, in which the reductive system of PCS and a Lewis base was adapted.

2 Deoxygenation of biomass derivatives

Deoxygenation is a chemical reaction, where an oxygen atom is removed from a molecule. In organic synthesis, it is frequently used in various processes, where different kinds of natural molecules and pharmaceutical products are prepared [8].

In recent years, several deoxygenative reactions and mechanisms have been researched, in the pursuit of the ability to efficiently convert biomass into more useful products. Plant-based lignocellulose, which consists of three polymers: cellulose, hemicellulose and lignin, could for example be turned into sugars and other polyoxygenated monomers, which in turn could then be deoxygenated to form new compounds [9]. Such processes could potentially have many industrial applications, especially in the areas of fuel, chemical and polymer production.

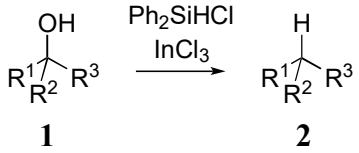
This chapter aims to provide a theoretical background, which would be used as the basis of the deoxygenation studies. The first part of the chapter describes various ways and mechanisms of cleaving C-O bonds, whereas the second section focuses on the reported pathways and procedures of deoxygenating alcohols. To limit the scope of the thesis work, mechanisms like decarbonylation and decarboxylation were not discussed, because they can not be utilized as pathways for the deoxygenation of alcohols.

2.1 Mechanisms of deoxygenation

2.1.1 Cleavage of C-O σ-bonds

The deoxygenation of secondary and tertiary alcohols was reported by Baba *et al.* [10]. In these reactions, various alcohols were treated with Ph_2SiHCl, using $InCl_3$ as catalyst. As the hydride delivery from Ph_2SiHCl enabled the hydroxyl group to act as a leaving group, the obtained products were the corresponding alkanes. Therefore the lack of an oxygen atom is the only molecular difference between the starting material and the product.

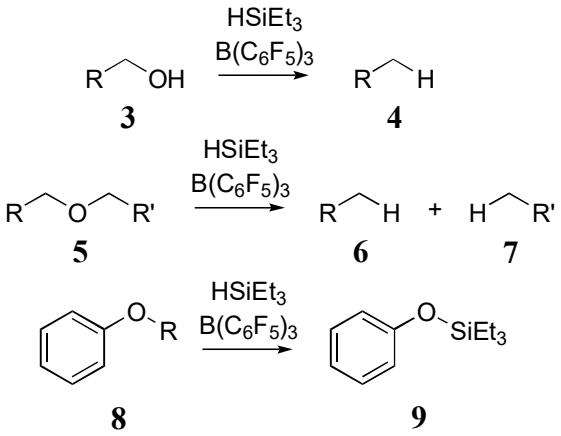
Although Baba *et al.* obtained the deoxygenated products in good yields, the procedure did not reduce primary alcohols [10]. Additionally, when the same procedure was applied to a 1-phenylbutane-1,4-diol, the corresponding primary alcohol was obtained as the major product, indicating that the deoxygenation method was highly selective towards secondary and tertiary hydroxyl groups. The procedure is illustrated in scheme 2.1.



Scheme 2.1: Deoxygenation of secondary and tertiary alcohols [10]

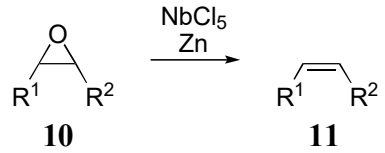
Another method, where primary alcohols were treated with $HSiEt_3$ and $B(C_6F_5)_3$, was reported by Gevorgyan *et al.* [11]. While the corresponding alkanes were obtained in good yields, similar results were not observed, when the procedure was applied to secondary and tertiary alcohols, although the deoxygenation of diphenylmethanol and triphenylmethanol was successfully observed.

In addition, Gevorgyan *et al.* also observed that the procedure can cleave and deoxygenate a variety of ethers [11]. Aliphatic ethers were deoxygenated to their corresponding alkane derivatives, even when cyclic structures were present. However, the reduction of aryl ethers was not observed, as aryl silyl ethers were formed instead, due to the cleavage of the ether bond. The reactions are presented in scheme 2.2.



Scheme 2.2: Deoxygenation of primary alcohols and aliphatic ethers, and the C-O cleavage of aryl ethers [11]

Oh and Knabe reported a method of deoxygenating epoxides, using $NbCl_5$ and Zn [12]. As the epoxides were reduced to their corresponding olefins, only the oxygen atom was removed, thus keeping the rest of the molecular structures intact. While the procedure was successfully applied to various substrates, many of the reactions formed mixtures of compounds, which had a negative effect on the yields of the desired products. The reaction times were also quite long for some substrates, as Oh and Knabe discovered that the reaction rates were much faster for aryl epoxides. The epoxide deoxygenation procedure is presented in scheme 2.3.

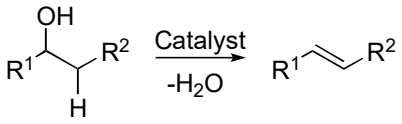


10 **11**

Scheme 2.3: Deoxygenation of epoxides [12].

2.1.2 Dehydration

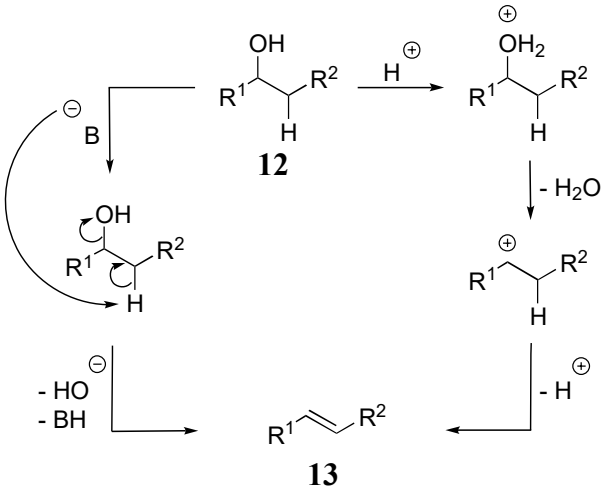
Dehydration is a deoxygenative reaction, where an alcohol is transformed to its corresponding olefin [5]. As the alcohol dehydrates into an olefin, a water molecule is also formed as a side product, which gives the reaction mechanism its name. The reaction is illustrated in scheme 2.4.



12 **13**

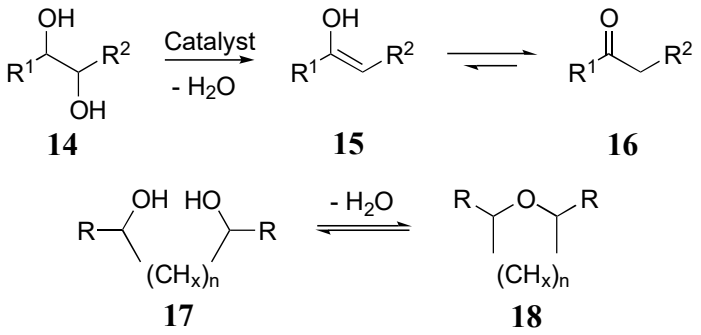
Scheme 2.4: The dehydration of an alcohol to an olefin. Adapted from literature [5]

According to ten Dam and Hanefeld, the dehydration reaction can be performed by acid or base catalysis [13]. Klein Gebbink *et al.* also reported that metal catalysts could be utilized in the dehydration of alcohols to olefins [14]. Although the end result would be the same, the reactions would transpire through different pathways. For example, the acid catalyzed reaction proceeds through an E_1 mechanism, whereas the base catalyzed reaction is an E_2 reaction [13]. The acid and base catalyzed mechanisms are displayed in scheme 2.5.



Scheme 2.5: Acid catalyzed and base catalyzed dehydration mechanisms. Modified from literature [13]

Ten Dam and Hanefeld also reported that it is possible to perform a dehydration reaction of diols [13]. The dehydration of a vicinal diol leads to the formation of **15**, which in turn can rearrange to an aldehyde or a ketone **16** via keto-enol tautomerism. Furthermore, a long-chain diol **17** can be dehydrated to form a cyclic ether **18**. These mechanisms are presented in scheme 2.6.



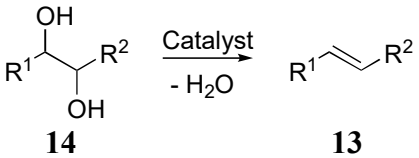
Scheme 2.6: Dehydration mechanisms for diols. Adapted from literature [13]

According to ten Dam and Hanefeld, even though diols are dehydrated quite easily, there are some issues that have to be taken into consideration [13]. For example, when **14** is dehydrated into **15**, it is difficult to selectively reduce a primary or a secondary hydroxyl group. Also, the problem with **17** dehydrating into **18** is that the process is reversible, as **18** can rehydrate back to **17**.

2.1.3 Deoxydehydration

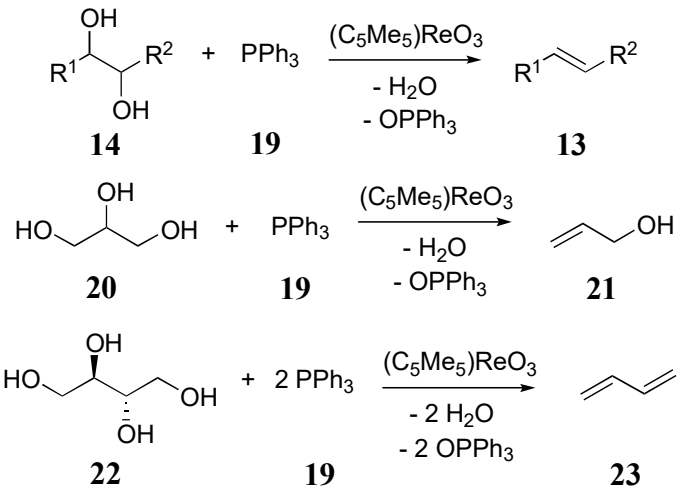
Deoxydehydration combines deoxygenation and dehydration into one mechanism. Gebbink *et al.* reported that the reaction can be used to transform vicinal diols into olefins, while obtaining water as a side product [14]. This is a significant change in comparison to the dehydration mechanism, which produced aldehydes and ketones from vicinal diols. The deoxydehydration reaction is illustrated in scheme 2.7.

Cook and Andrews reported the transformation of vicinal diols into *trans*-olefins, using $(C_5Me_5)ReO_3$ as catalyst [15]. In addition, triphenylphosphine was used in the reaction



Scheme 2.7: Deoxydehydration of a vicinal diol to an olefin. Adapted from literature [14]

as a reducing agent and the reaction temperatures were between 90-135 °C. The reaction performed well for various substrates, affording the intended products in high yields. The method was also successfully applied for glycerol and erythritol, indicating the potential of performing effective reductions to polyols. Scheme 2.8 illustrates the reaction equations.



Scheme 2.8: Deoxydehydration of vicinal diols, glycerol and erythritol with $(C_5Me_5)ReO_3$ and triphenylphosphine. Modified from literature [15]

Catalyst instability issues, along with a relatively expensive process are some of the difficulties reported by Cook and Andrews [15]. Additionally, they determined that for more complex polyols, it was challenging to control or predict the regioselectivity of the reaction.

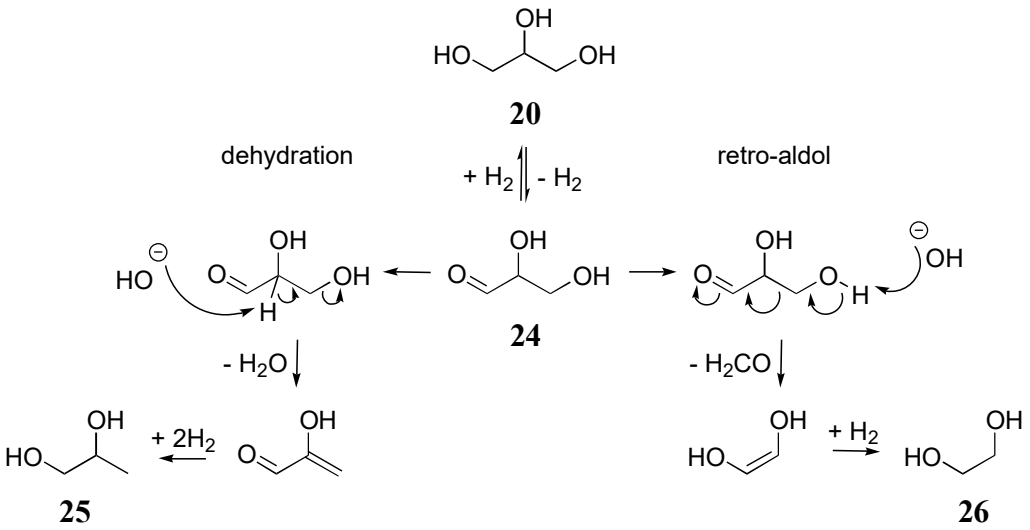
According to a review by Sousa and Fernandes, similar reactions with different catalysts and reductants have also been reported in literature [8]. For example, studies have been conducted using various rhenium-derived compounds as catalysts and alcohols, hydrogen and sulfides as reductants.

2.1.4 Hydrogenation and hydrogenolysis

Hydrogenation is a process, where two hydrogen atoms are added to a molecule, in such a way that does not result in any bond cleavage [16]. Usually hydrogenation only occurs, whenever unsaturated bonds are present in a compound. For example, double bonds can be hydrogenated into single bonds and triple bonds can be hydrogenated into double bonds.

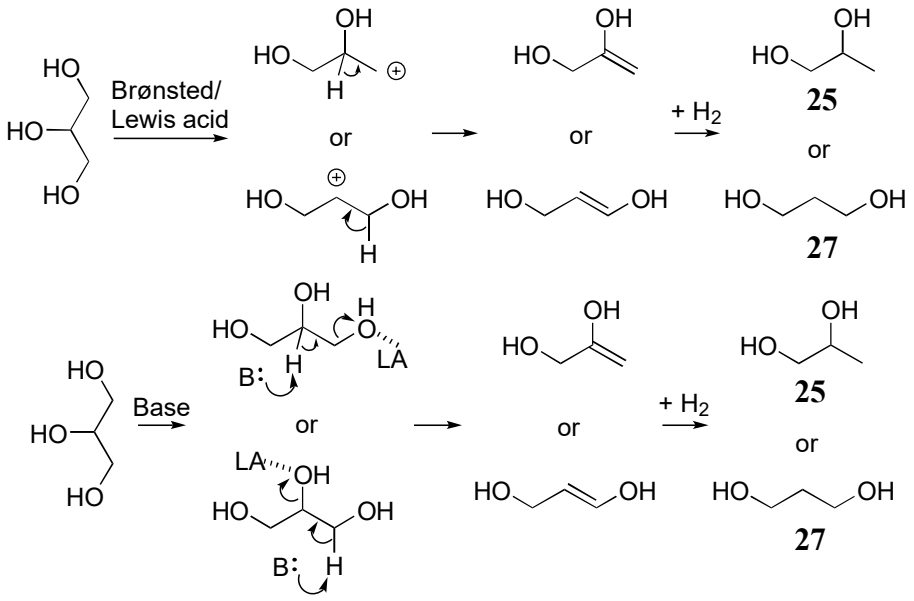
Hydrogenolysis, on the other hand, is a reaction, where carbon-carbon or carbon-heteroatom single bonds are cleaved with hydrogen [16]. As both processes require hydrogen as a reagent, it can in some instances be possible for both mechanisms to take place during the same reaction.

The hydrogenolysis of polyols, using ruthenium-based compounds and Raney copper as catalysts, was reported by Montassier *et al.* [17]. For example, they observed the transformation of glycerol into 1,2-propanediol and ethylene glycol, which led to the proposal that the hydrogenolysis mechanism can be divided into three parts: dehydrogenation of the starting material, *in situ* deoxygenation and the hydrogenation of the forming products. They also suggested that the hydrogenolytic deoxygenations would transpire via dehydration, retro-aldol, retro-Claisen or retro-Michael mechanism, although the retro-Claisen and retro-Michael pathways have since been questioned by other researchers [16]. The hydrogenolysis mechanisms are displayed in scheme 2.9.



Scheme 2.9: The three-step hydrogenolysis of glycerol via dehydration and retro-aldol mechanisms, catalyzed by adsorbed hydroxyl groups from metal surface. Modified from literature [17]

Palkovits *et al.* also presented multiple reactions for the hydrogenolysis of glycerol in their review [16]. In their proposed mechanisms, glycerol hydrogenolysis is catalyzed by a Brønsted acid or a Lewis acid. Lewis acid assisted Brønsted base catalysis was also suggested. The products that were obtained were either 1,2-propanediol or 1,3-propanediol. These mechanisms are demonstrated in scheme 2.10.

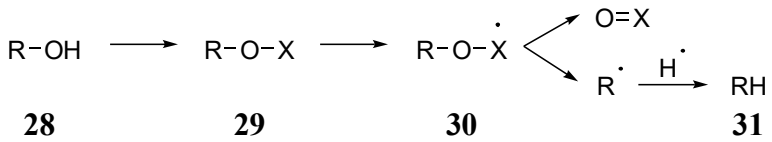


Scheme 2.10: Glycerol hydrogenolysis, catalyzed by Brønsted acid, Lewis acid or a Lewis acid/Brønsted base system. Adapted from literature [16]

2.1.5 Radical mechanisms

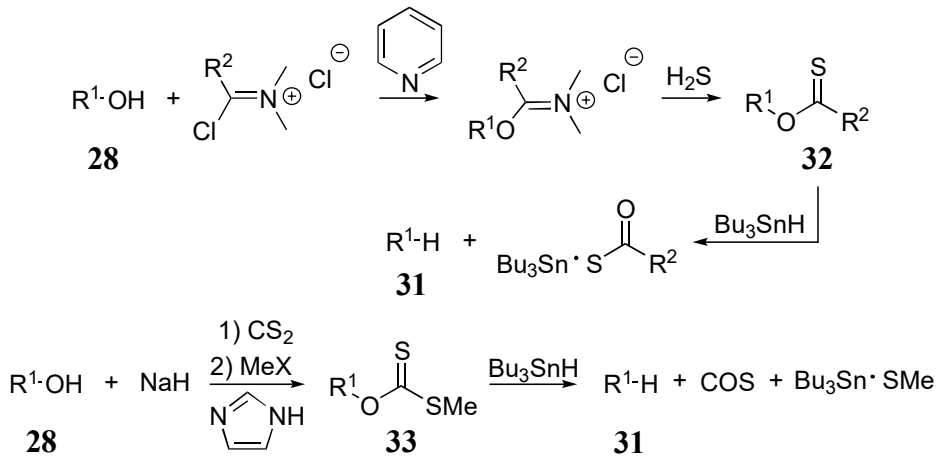
Some deoxygenation mechanisms take advantage of highly reactive free radical moieties. According to Hartwig, radicals are less affected by steric hindrances and radical reactions can be performed in neutral conditions, therefore providing a possible mechanism for compounds that are extremely sensitive [18]. Also, radical reactions do not promote unwanted eliminations and rearrangements, which are typical in ionic mechanisms, where a carbocation intermediate is formed.

Hartwig proposes that radical deoxygenation is based on a C-O bond undergoing homolytic cleavage, which means that the bond is cleaved so that both atoms retain one free electron [18]. For alcohols, such manipulations are performed by first functionalizing the alcohol, which is then turned into an intermediate radical species that is cleaved. The resulting alkyl radical then accepts a proton from a donor, thus resulting in the corresponding alkane. The mechanism is illustrated scheme 2.11.



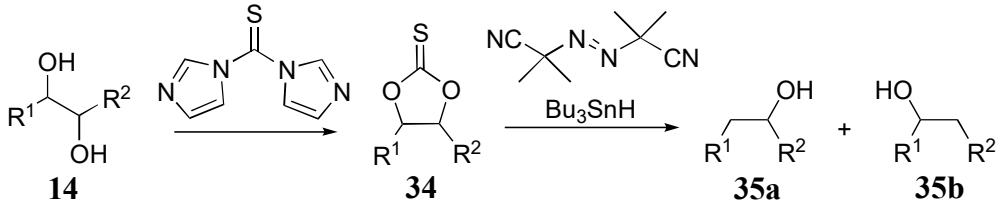
Scheme 2.11: General mechanism of the radical deoxygenation of alcohols, where intermediate **30** undergoes homolytical cleavage. Adapted from literature [18]

The most famous radical deoxygenation mechanism is the Barton-McCombie deoxygenation, where a secondary alcohol derivative is treated with tri-*n*-butyltin hydride, to give the corresponding deoxygenated product [4]. The derivatives that were used in the reactions were either thionoesters or xanthates, which are O-alkyl thioesters and dithiocarbonate-derived O-esters, respectively. The functionalizations and the following deoxygenations are presented in scheme 2.12.



Scheme 2.12: Barton-McCombie deoxygenation of thionoester **32** and xanthane **33**. Modified from literature [4]

The toxicity of stannanes and the difficulties in product purification are the main issues in the Barton-McCombie deoxygenation process [5]. Furthermore, the procedure could not be successfully applied to primary alcohols [4]. However, despite the several problems regarding the Barton-McCombie deoxygenation, it has inspired numerous studies of the reaction. According to Crich and Quintero, the Barton-McCombie mechanism has not only been tested for various secondary alcohol derivatives, as attempts of applying the method to diols and triols have also been performed [19]. For example, when a diol reacts with thiocarbonyldiimidazole, a cyclic thiocarbonate intermediate is formed, after which treatment with azobis(isobutyronitrile) and tri-*n*-butylstannane in 110 °C affords two monoalcohols as products. This reaction is displayed in scheme 2.13.



Scheme 2.13: Barton-McCombie deoxygenation of diol **14** to monoalcohols **35a** and **35b**. Modified from literature [19]

Using the method presented in scheme 2.13, Barton and Subramanian performed deoxygenations to various polycyclic 1,2- and 1,3-diols [20]. According to their observations, the reactions favored the deoxygenation of the secondary hydroxyl group and the formation of a primary alcohol, therefore exhibiting good regioselective properties. This regioselectivity is based on the fact that the Barton-McCombie mechanism does not deoxygenate primary alcohols.

However, Barton and Subramanian added that when the cyclic thiocarbonate was prepared from a diol that had two secondary hydroxyl groups, mixtures of products were obtained due to reduced selectivity [20]. In spite of this, some selectivity was still observed, as the deoxygenation of a secondary hydroxyl group in a sterically hindered position was slightly less favorable.

2.2 Deoxygenation of alcohols

This chapter focuses on the different synthetic pathways of deoxygenating alcohols. For each pathway, selected examples of works that have been carried out in recent years are presented. In general, the deoxygenations of alcohols can be divided into three main categories: direct deoxygenations, two-step deoxygenations and Lewis acid catalyzed deoxygenations.

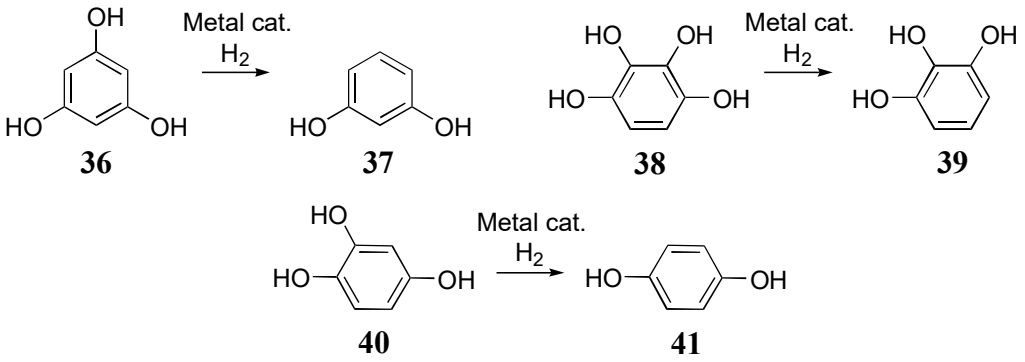
2.2.1 Direct deoxygenation

The direct deoxygenation of an alcohol means that the deoxygenated product is obtained after only one synthetic step. This would be the most convenient way of obtaining diffrerent products from alcohols, therefore making such methods extremely sought after. For example, these methods would save chemicals, money and time, which would especially be of interest from an industrial point of view [5].

The direct deoxygenations of monoalcohols were already presented in section 2.1.1. Baba *et al.* reported the deoxygenation of secondary and tertiary alcohols with Ph_2SiHCl and $InCl_3$ [10], whereas Gevorgyan *et al.* used $HSiEt_3$ and $B(C_6F_5)_3$ to reduce primary alcohols.

Hansen and Frost reported the direct monodeoxygenation of polyhydroxybenzenes, using rhodium, platinum and palladium catalysts [21]. The reactions transpired via a hydrogenation mechanism and the reactions were carried out under a hydrogen pressure of

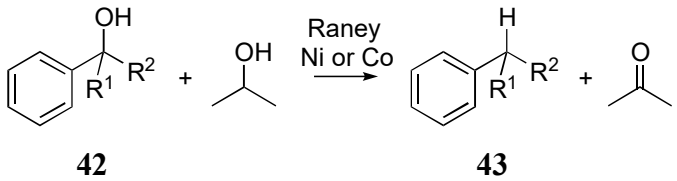
50 psi. Depending on the starting material, the products were either di- or trihydroxylated benzenes. The reactions are displayed in scheme 2.14.



Scheme 2.14: Direct hydrogenations of phloroglucinol **36** into resorcinol **37**, 1,2,3,4-tetrahydroxybenzene **38** into pyrogallol **39** and hydroxyhydroquinone **40** into hydroquinone **41**. Adapted from literature [21]

The main issue with the method presented by Hansen and Frost is that it only applies for specific polyhydroxybenzenes. Therefore, the amount of potential synthetic applications is somewhat limited for this reaction.

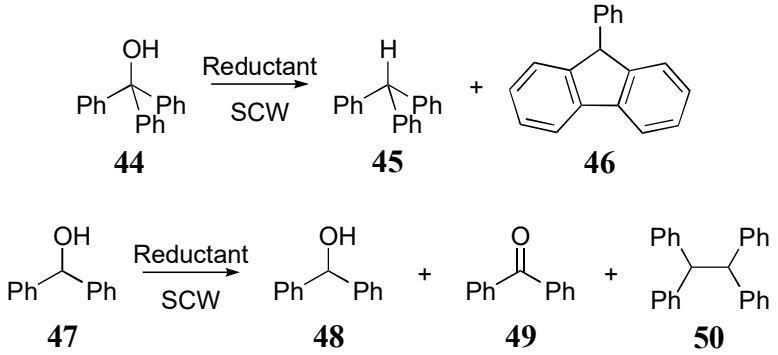
Mebane *et al.* reported a process, where a variety of primary, secondary and tertiary aromatic monoalcohols were deoxygenated using a direct transfer hydrogenolysis reaction [22]. Using Raney nickel and Raney cobalt as catalysts and refluxing 2-propanol as the hydrogen donor, they were able to transform a variety of benzylic and non-benzylic aromatic alcohols into their deoxygenated counterparts. The 2-propanol is transformed into acetone, which is the major side product of the reaction, along with water. For some substrates, the formation of small amounts of side products was observed. The process is illustrated in scheme 2.15.



Scheme 2.15: Transfer hydrogenolysis of aromatic monoalcohol **42** to deoxygenated compound **43**. Modified from literature [22]

A procedure of directly reducing di- and triphenylmethanol in supercritical water was reported by Kobiro *et al.* [23]. The process also used a sugar, an alcohol or an aldehyde as a reductant, while also requiring very high temperatures to afford any deoxygenation

products. Although the reaction was extremely fast, it usually resulted in mixtures of products in varying quantities. However, in many of the reactions, the hydroxyl cleaved compound was the major product. The reactions are presented in scheme 2.16.

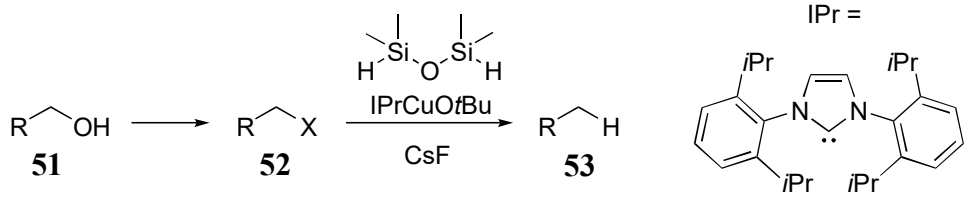


Scheme 2.16: Direct deoxygenation of di- and triphenylmethanol in supercritical water. Adapted from literature [23]

2.2.2 Two-step deoxygenation

Because the bond between carbon and oxygen is quite strong, it is very difficult to perform deoxygenations in mild conditions [5]. For this reason, it is often challenging to selectively deoxygenate hydroxyl groups, as harsher deoxygenation methods usually suffer from reduced selectivity [2]. For that reason, alcohols are often reduced in two steps, where the alcohol is first transformed into a desireable intermediate, which is then subjected to a reductive process. For example, many of the deoxygenation methods of alcohols presented in section 2.1 fulfill this criteria.

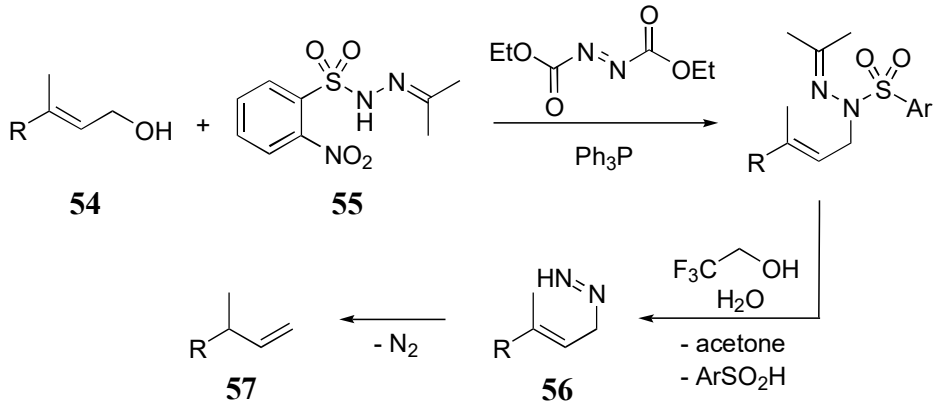
Lalic *et al.* presented a procedure for the deoxygenation of primary triflates or primary and secondary iodides [24]. The procedure uses a copper-based compound as catalyst, tetramethyldisiloxane as a hydride source and cesium fluoride as a catalyst enhancing additive. The corresponding deoxygenated products were obtained in high yields. Scheme 2.17 demonstrates the procedure.



Scheme 2.17: Copper-catalyzed deoxygenation of triflate or iodide **52** into **53**. Adapted from literature [24]

The method developed by Lalic *et al.* showcases the potential in derivatizing alcohols for deoxygenative purposes. By first functionalizing the hydroxyl group of **51** into something that acts as a better leaving group, the alcohols are reduced efficiently under milder conditions, which translates to improved selectivity [24]. The additional synthetic steps required to prepare the derivatives are naturally a drawback in comparison to the direct deoxygenation methods.

Movassaghi and Ahmad developed a method, where a primary or a secondary alcohol is deoxygenated with *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazine and treated with triphenylphosphine and diethyl azodicarboxylate, which are commonly used in Mitsunobu reactions [25]. The reaction produces a monoalkyl diazene intermediate, which is then transformed to the desired deoxygenation product via hydrolysis in 2,2,2-trifluoroethanol. Alkyl alcohols were transformed into their corresponding alkyl compounds, whereas deoxygenation and double bond transposition was observed for allyl alcohols. Secondary alcohols with terminal triple bonds were deoxygenated and transformed into terminal allenes. The reaction is illustrated in scheme 2.18.

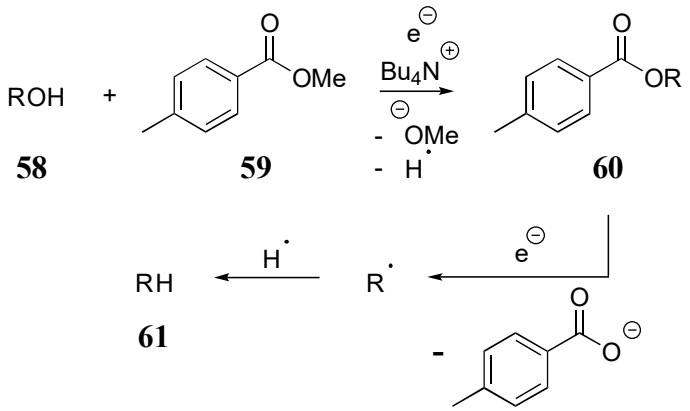


Scheme 2.18: Transformation of alcohol **54** to **57** via intermediate **56**, using *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazine **55**. Modified from literature [25]

Lam and Markó discovered a radical mechanism, where primary alcohols are reduced to their corresponding alkanes in the presence of tetra-*n*-butylammonium ion electrolytes and an excess of methyl toluate, using electricity as the driving force [26]. The deoxygenation occurred via electrotransesterification, where an electrically deprotonated alcohol is first transesterified with methyl toluate, to give a stable intermediate. The intermediate ester is then electrically cleaved, so that the desired alkane is obtained. The process is displayed in scheme 2.19.

According to Lam and Markó, the main benefit of the reaction is its ability to reduce unfunctionalized alcohols [26]. Several non-hydroxyl functional groups were also unaf-

fected, producing the desired result selectively, even when the reactions were scaled up to gram scale. However, tests were also conducted on secondary and tertiary alcohols, but no significant product formation was observed. The procedure also suffers from a low degree of efficiency, because the current efficiency percentages were quite unfavorable, and as an excess of methyl toluate was needed due to unintended electrolysis.



Scheme 2.19: Electrochemical conversion of primary alcohol **58** to **61**. Modified from literature [26]

2.2.3 Lewis acid catalyzed deoxygenation

Lewis acids are defined as compounds that can accept an electron pair, whereas Lewis bases can donate an electron pair [27]. G.N. Lewis' proposal is considered an alternative to the Brønsted-Lowry definition, which states that acids act as proton donors and bases act as proton acceptors [27].

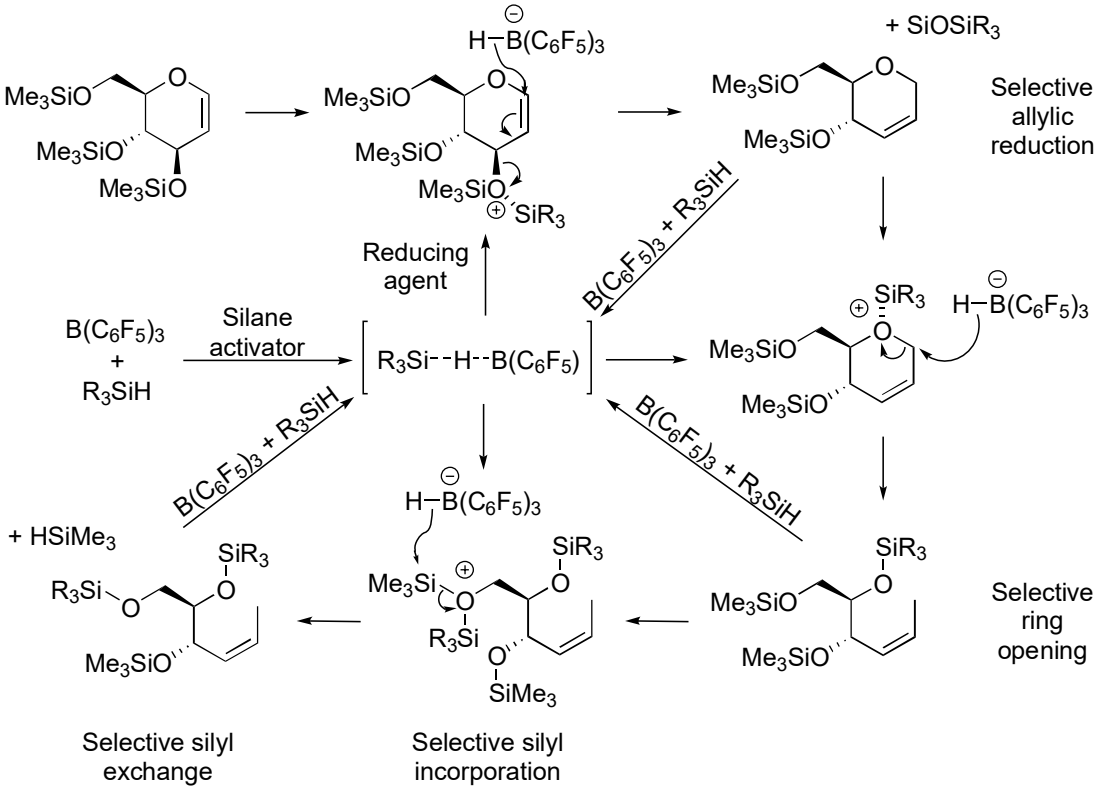
The reduction of alcohols with hydrosilanes and chlorohydrosilanes has been studied intensively during the course of the past few years. It has been observed that the combination of a Lewis acid catalyst and a hydrosilane can be employed in the reduction of different moieties, such as unsaturated carbon-carbon bonds, carbonyl groups, hydroxyl groups and ethers [11]. These systems are especially of interest in the deoxygenation of alcohols, in the pursuit of the development of selective and highly efficient reductive processes, which could be applied to a variety of alcohols, regardless of their degree of functionalization [10]. The Lewis-acid catalyzed methods that were developed by Baba *et al.* and Gevorgyan *et al.* were already presented in section 2.1.1.

In the late 1990s, it was observed that tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, acted as a Lewis acid catalyst in the hydrosilane-mediated reduction of carbon-heteroatom double bonds [6]. It was later discovered that $B(C_6F_5)_3$ activated the hydrosilane for hydride

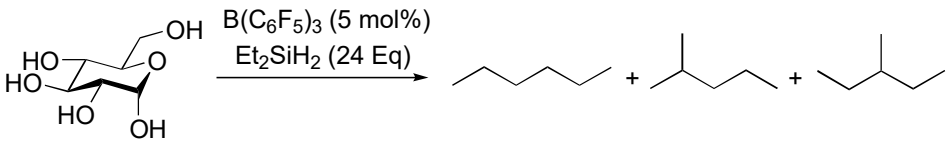
delivery, instead of coordinating to the carbon-heteroatom bond. This was a significant discovery, as it allowed the procedure to be extended to a variety of functional groups.

In 2016, Gagné *et al.* examined the reductions of silylated polyols with $B(C_6F_5)_3$, while also showcasing its multifunctional catalytic properties [28]. They discovered that, in addition to being an activator for hydrosilanes, $B(C_6F_5)_3$ can activate allylic silyl ethers as an oxophilic Lewis acid, catalyzing the formation of heterocyclic compounds. They were also able to show that the $B(C_6F_5)_3$-hydrosilane system had specific regio- and chemopreferences, thus offering the possibility of highly selective molecular manipulations. Scheme 2.20 illustrates the multifunctionality of $B(C_6F_5)_3$.

Gagné *et al.* also studied the process of directly deoxygenating entire sugar molecules, using Et_2SiH_2 and $B(C_6F_5)_3$ [29]. While they achieved the complete deoxygenation of a polyoxygenated starting material, they obtained a mixture of different products, depending on which starting material was used. For example, glucose was deoxygenated into a mixture, where *n*-hexane, 2-methylpentane and 3-methylpentane were the majority products with a yield of about 30% each. Some olefin isomers were also obtained as minor side products. The complete reduction of glucose is displayed in scheme 2.21.



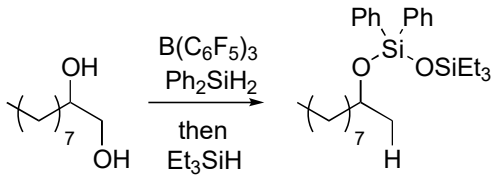
Scheme 2.20: The multiple roles of $B(C_6F_5)_3$ in the deoxygenation of silylated polyols. Adapted from literature [28]



Scheme 2.21: Direct, complete deoxygenation of glucose with $B(C_6F_5)_3$ and Et_2SiH_2. Adapted from literature [29]

Although the complete deoxygenation of sugar molecules is an impressive display of the reductive power of $B(C_6F_5)_3$-catalyzed hydrosilane systems, the practical uses of the process seem quite limited. If it was possible to perform partial deoxygenations, or if it was possible to obtain products in a more selective fashion, the reaction would certainly be utilized more in different applications.

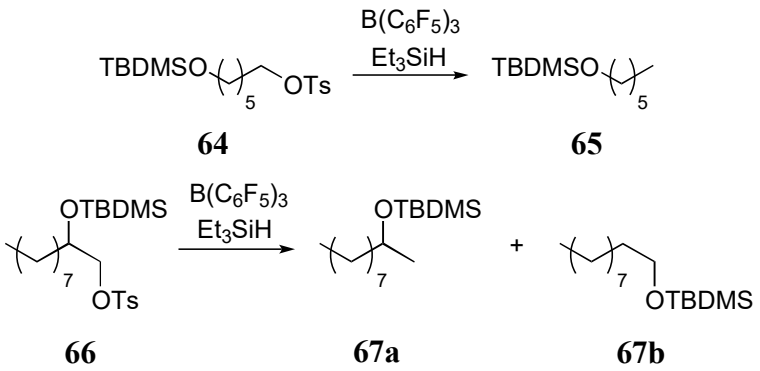
Drosos and Morandi reported the selective deoxygenation of the primary hydroxyl group of 1,2-diols, using $B(C_6F_5)_3$ and a combination of Ph_2SiH_2 and Et_3SiH [30]. They observed that the reaction transpires via a cyclic siloxane intermediate, which is the key factor behind the selectivity of the reaction. The procedure was successfully applied to a variety of substrates, including an extension to butane-1,3-diol, and the products were obtained in moderate to high yields. In addition, Drosos and Morandi observed that the procedure could be applied to enantiomerically pure compounds, with racemization of the tertiary stereogenic centre, thus enabling the opportunity of using the reaction as a part of an asymmetric synthesis. The reaction is illustrated in scheme 2.22.



62 **63**

Scheme 2.22: Deoxygenation of the primary hydroxyl group of decane-1,2-diol. Adapted from literature [30]

In a recent paper, Oestreich *et al.* reported the selective deoxygenation of various tosylates, using $B(C_6F_5)_3$ and Et_3SiH [31]. Various alkyl and aryl tosylates were successfully cleaved, to give the corresponding deoxygenated product in a highly selective fashion. Although the procedure isn't as convenient as the reaction reported by Drosos and Morandi, due to the added step of preparing the tosylates, the process exhibits remarkable tolerance towards a variety of different functional groups. The process is displayed in scheme 2.23.

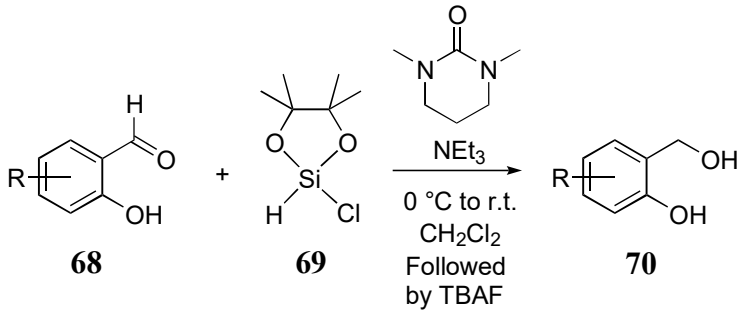


Scheme 2.23: Deoxygenation of alcohol-derived tosylates. The ratio of **67a** and **67b** was (53:47). Adapted from literature [31]

2.3 Reduction with pinacol-derived chlorohydrosilane

Recently, Assoah and co-workers developed a novel method, where salicylaldehyde derivatives are reduced to their corresponding primary alcohols, using a pinacol-derived chlorohydrosilane (PCS) [7]. They observed that PCS can be attached to the hydroxyl group of a salicylaldehyde to form a hydrosilyl ether, after which a Lewis base catalyst would activate the silicon centre, leading to a hydride delivery to the carbonyl group. The reaction resulted in a stable bicyclic silyl ether intermediate, which would be transformed to the desired alcohol via desilylation and protonation.

After extensive testing, Assoah *et al.* chose 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as the Lewis base activator for PCS, as it proved to give the best results [7]. Triethylamine was also used to neutralize hydrochloric acid. The process is illustrated in scheme 2.24.



Scheme 2.24: Selective reduction of salicylaldehyde **68** into alcohol **70**, using PCS **69**. Adapted from literature [7]

Assoah and co-workers also successfully applied the PCS-procedure to 2-hydroxyacetophenone, which was reduced to 2-(1-hydroxyethyl)phenol, although the product was

obtained at a slightly lower yield [7]. Significant selectivity properties were also observed, as the procedure proved to selectively reduce the aldehyde moieties that were in the ortho-phenol position, even in the presence of other aldehyde or ketone moieties. In addition, the PCS-process was utilized in the reductive amination of salicylaldehyde with indoline, thus proving that the system of PCS and a Lewis base can catalyze a variety of reductive reactions.

Even though advances in the pursuit of effective and selective methods for the deoxygenation of polyols have been made, it is still extremely challenging. Therefore, it was decided to experiment on the deoxygenation of alcohols. As it appeared that there were many limitations in the direct deoxygenation methods, including a narrow substrate scope and conditions that were difficult to replicate in a synthesis laboratory environment, the two-step methods via alcohol derivatization were chosen to be experimented on. Based on the available literature, it seemed reasonable to decide that the deoxygenations should be performed via hydrosilylation, as those reactions exhibited interesting selective characteristics.

However, it was decided to not use the $B(C_6F_5)_3$-Lewis acid reducing system. Instead, inspired by the results obtained by Assoah *et al.*, it was decided that the PCS-Lewis base combination should be used instead, as it was interesting to see if the reducing capability could be extended to diols. It was also interesting to learn, how PCS tolerates different functional groups, in contrast to the reported capabilities of $B(C_6F_5)_3$.

Decane-1,2-diol was chosen as the starting material for the studies, as it provided a challenging environment to experiment on, and because it was commercially available. The main goal was to selectively deoxygenate the secondary hydroxyl group of decane-1,2-diol, as the selective deoxygenation of the primary hydroxyl group of vicinal diols was already reported in literature [30]. The envisioned products also have a rather high boiling point, thus allowing their isolation without significant losses during purification of the reaction mixtures. The decane-1,2-diol derivatives were also of interest in another study, where the biological activity of long-chain diol derivatives as anti-cancer agents was examined [32].

3 Alcohols

Alcohols are classified as hydrocarbons, which contain at least one hydroxyl group. They are widely used throughout the field of organic chemistry, as solvents, reagents and eluents. They are also useful synthetic building blocks, as many compounds, such as aldehydes, ketones, carboxylic acids, esters and alkyl halides, can be prepared using an alcohol as the starting material. As was previously presented in section 2, alcohols can also be deoxygenated to produce even more products.

Diols are alcohols that have two hydroxyl groups in their molecular structures and triols have three hydroxyl groups, analogously. Like most alcohols, they can present themselves in various regioisomers, the properties of which can vary vastly from one isomer to another. Structurally, diols can be divided into four main categories: geminal, vicinal, terminal and n,m-diols. In a geminal diol, the hydroxyl groups are attached to the same carbon atom, whereas the hydroxyl groups are located in two adjacent carbons in a vicinal diol. A terminal diol has two primary hydroxyl groups that are located at the very ends of an aliphatic chain, while in a n,m-diol the hydroxyl groups are located in two different non-adjacent carbons.

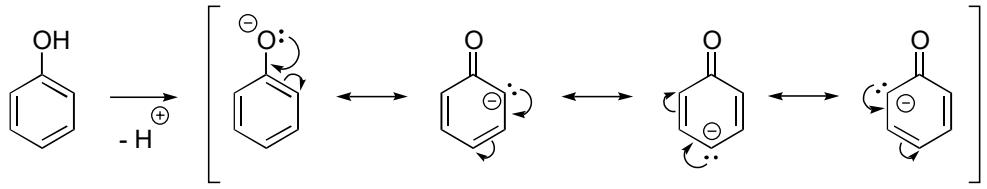
Polyol is a broader term, which is used to describe alcohols that have more than two hydroxyl groups. Various sugars, such as glucose and fructose, are good examples of such polyhydroxylated compounds.

3.1 Properties of alcohols

Alcohols are polar compounds, because an oxygen atom has more electronegativity than a carbon or a hydrogen atom. However, because of this difference in electronegativity between the oxygen and the hydrogen, an alcohol molecule can bond to another alcohol molecule via hydroxyl group mediated hydrogen bonding [27]. Even though hydrogen bonds are not as strong as ionic or covalent bonds, they are strong enough to significantly affect the chemical properties of alcohols. For example, alcohols have higher boiling points than ethers and non-oxygenated hydrocarbons with similar structures, while also exhibiting a high degree of water solubility [27]. However, the larger the hydrocarbon is in relation to the hydroxyl group, the less the alcohol is soluble in water.

Alcohols can act as weak Brønsted acids or bases [27]. The deprotonation of an alcohol affords an alkoxide ion, whereas the protonation of an alcohol affords an alkyloxonium

ion. Furthermore, as the oxygen atom has two non-bonding electron pairs, an alcohol can also be classified as a Lewis base [27]. However, the acidity properties can differ greatly between different alcohols. For example, phenol, which is an aromatic alcohol that has a hydroxyl group bonded directly to the aromatic ring, has a pK_a value of 10.0, whereas the pK_a of ethanol is 15.9, which shows that phenol is significantly more acidic [27]. The conjugate base of phenol is the phenoxide ion, which can partially stabilize its structure via resonance, which in turn increases phenol's acidity. This is illustrated in scheme 3.1.



Scheme 3.1: The resonance structures of the phenoxide ion. Adapted from literature [27]

Alcohols can can have hydroxyl groups attached to a primary, secondary or tertiary carbon atom. Depending on the mechanism of a reaction, these hydroxyl groups have significant differences in their reactivities. For example, a primary hydroxyl group always reacts via the S_N2 mechanism, because of the instability of the required primary carbocation intermediate [33]. The S_N1 mechanism is preferred for tertiary hydroxyl groups, because the corresponding carbocation is much more stable than the primary intermediate. However, as a tertiary hydroxyl group is much more sterically hindered than a primary hydroxyl group, it should never react in an S_N2 reaction [33]. The reactivity of the secondary alcohols is the most difficult to predict, as both S_N1 and S_N2 mechanisms are possible for a secondary hydroxyl group, due to less steric hindrance in comparison to a tertiary hydroxyl group, and the secondary carbocation being more stable than the primary intermediate.

Because the hydroxyl group is a bad leaving group, the C-O bond in alcohols can not be eliminated directly. Instead, the eliminations usually employ dehydration mechanisms, which were already discussed in section 2.1.2, or strategies, where the hydroxyl group is converted into a better leaving group prior to elimination [34]. This is yet another area, where the different reactivities of primary, secondary and tertiary hydroxyl groups play an important role. For example, in reactions where an alcohol acts as a nucleophile and reacts with an electrophile, primary hydroxyl groups are more reactive than secondary hydroxyl groups, which in turn are more reactive than tertiary hydroxyl groups [35]. Furthermore, steric hindrance always has a negative effect on alcohol reactivity. As an example, if a molecule has two secondary hydroxyl groups, but one of them is sterically hindered, the less hindered group is more reactive. The difference in hydroxyl group reactivities is vital, when selective synthesis pathways are planned for diols and polyols.

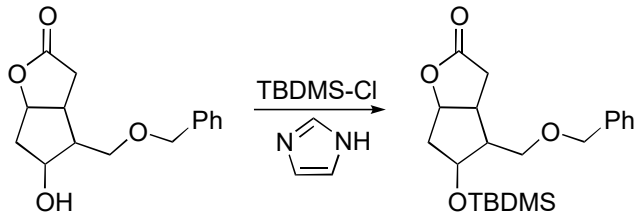
3.2 Alcohols in reactions

In chapter 2, various ways of preparing products via alcohol deoxygenation were discussed. However, as alcohols are incredibly versatile compounds, a further examination into their synthetic behaviour is warranted. The goal of this section is to provide ideas and insights for the planned selective derivatizations of decane-1,2-diol.

3.2.1 Protection of hydroxyl groups

Transforming alcohols into silyl ethers is one of the most common methods of protecting hydroxyl groups. By treating alcohols with silyl groups, the hydroxyl groups are protected from nucleophiles and carbon or nitrogen bases [35].

In 1972, Corey and Venkateswarlu presented a method, where alcohols were protected as *tert*-butyldimethyl silyl (TBDMS) ethers [36]. The procedure was carried out using *tert*-butyldimethyl silyl chloride and the reaction also required imidazole as a base catalyst. The process is displayed in scheme 3.2.



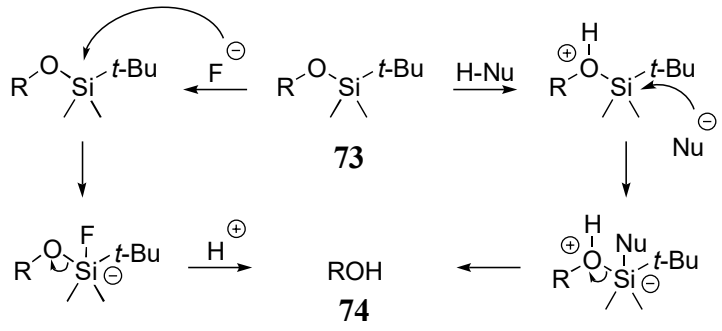
71 **72**

Scheme 3.2: The TBDMS-protection of compound **71**. Adapted from literature [36]

In addition to TBDMS, there are many other silyl groups, such as the trimethylsilyl, *tert*-butyldiphenyl silyl, dimethylisopropyl silyl and triisopropyl silyl groups, that can be used for the protection of alcohols in similar fashion. The different silyl groups naturally have vastly different properties, which is something that needs to be taken into account in synthesis planning. For example, Corey and Venkateswarlu observed that the trimethylsilyl group is quite easily detached via solvolysis, whereas dimethylisopropyl silyl and *tert*-butyldimethyl silyl are 10^2-10^3 and 10^4 times more stable in protic media, respectively [36].

Corey and Venkateswarlu were also able to show that the TBDMS-protected alcohols **72** can be deprotected with either fluoride anions or with acids [36]. The deprotection mechanism proceeds through a pentacoordinated silyl intermediate, which decomposes to

afford the desired alcohol. The two deprotection routes are demonstrated in scheme 3.3.

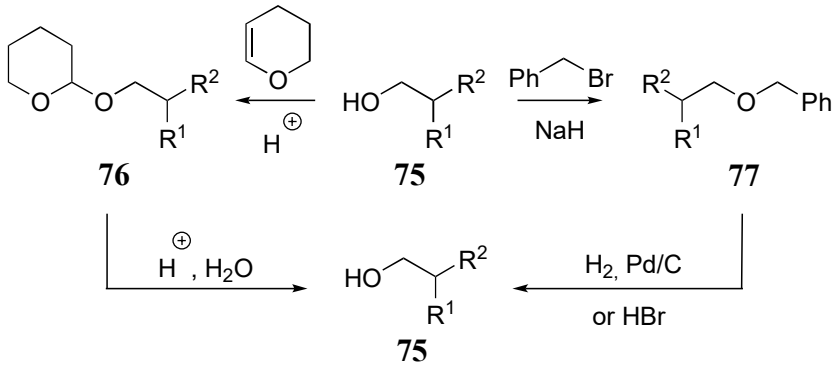


Scheme 3.3: The deprotection of **73** into alcohol **74**. Modified from literature [35]

In addition to the methods that were presented in scheme 3.3, methanol can also be used, when the more labile trimethylsilyl group needs to be removed [35]. Analogously, when extremely stable silyl groups are used to protect alcohols, the deprotection has to be performed with hydrofluoric acid [35].

Transforming hydroxyl groups into a tetrahydropyranyl group or a benzyl ether group are examples of alternative protection strategies. Treating an alcohol with dihydropyran in an acidic media results in the transformation of the hydroxyl group into a tetrahydropyranyl group, which protects an alcohol from strong bases and can be removed with aqueous acids [35]. Likewise, the strong base-mediated reaction between an alcohol and benzyl bromide results in the formation of the benzyl ether, which is an extremely strong protecting group, as it protects an alcohol from almost anything [35].

The downside in the tetrahydropyranyl group is that it offers a very narrow range of protection, as it only protects against strong bases. In turn, the issue in benzyl ether protection is that the options for the following deprotection are quite limited, as palladium-mediated hydrogenolysis or treatment with hydrogen bromide are the only commonly available deprotection methods [35]. These pathways are displayed in scheme 3.4.



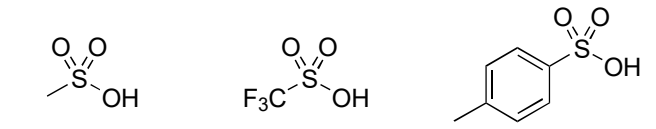
Scheme 3.4: The transformation of alcohol **75** into **76** or **77**, and their corresponding deprotections. Modified from literature [35]

Since the plan was to selectively deoxygenate the secondary hydroxyl group of decane-1,2-diol via a PCS-mediated two-step mechanism, it was necessary to develop a plan of protecting the primary hydroxyl group, so that the secondary hydroxyl group could be derivatized. After evaluating the available options, the TBDMS-protection appeared to be the most suitable method, as it offered good protective properties against the conditions of the envisioned functionalization reactions. The efficiency and the reported ease of the protection and the deprotection reactions was also a factor that affected the decision of choosing TBDMS as the protecting group [36].

3.2.2 Synthesis of alcohol derivatives

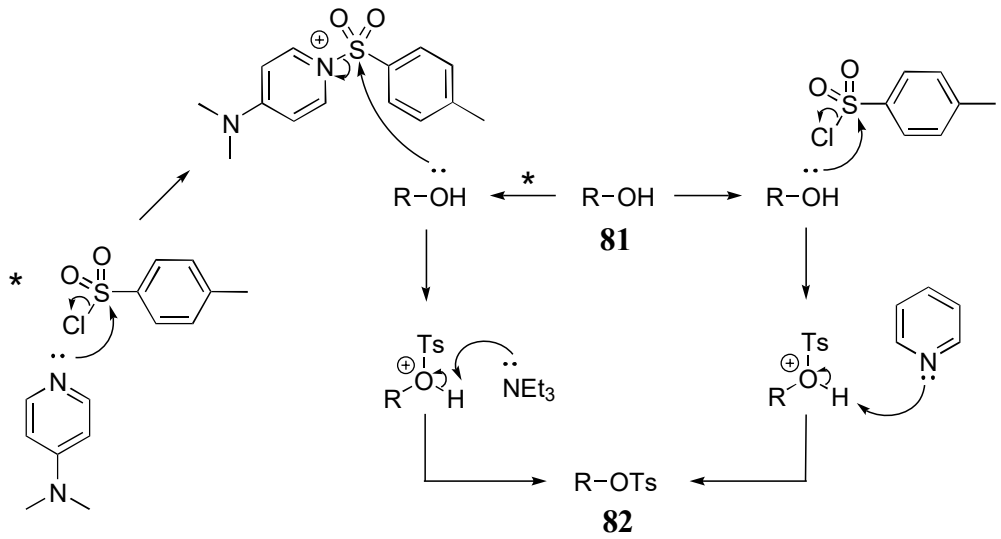
As was already mentioned, alcohols are extremely useful as synthetic building blocks, because a variety of different products can be prepared from them. However, as the interest was on performing selective deoxygenations of vicinal diol derivatives, it was determined that many of these synthetic pathways would fall out of the scope of this thesis work project. Therefore, in order to research ways of converting hydroxyl groups to better leaving groups, only reactions that feature an alcohol reacting as a nucleophile were examined.

One of the most commonly used methods of modifying hydroxyl groups is to transform them to sulfonate esters, such as *p*-toluenesulfonates, trifluoromethanesulfonates and methanesulfonates, which are also called tosylates, triflates and mesylates, respectively. The reason why these sulfonates make for such good leaving groups is because they are the weak conjugate bases of very strong sulfonic acids [37]. The corresponding sulfonic acids and their pK_a values are displayed in scheme 3.5.



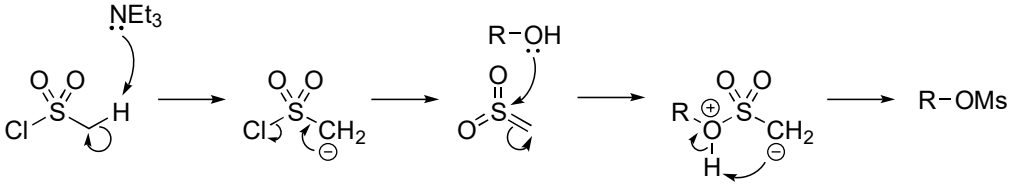
Scheme 3.5: Methanesulfonic, trifluoromethanesulfonic and *p*-toluenesulfonic acids and their reported pK_a values in different conditions. Modified from literature [37] [38]

Alcohols can be treated with tosyl chloride and pyridine, to give the corresponding tosylate [34]. Another known method for the tosylation is using tosyl chloride in the presence of 4-dimethylaminopyridine, while also using triethylamine to neutralize the forming hydrochloric acid[39]. The two mechanisms are illustrated in scheme 3.6.



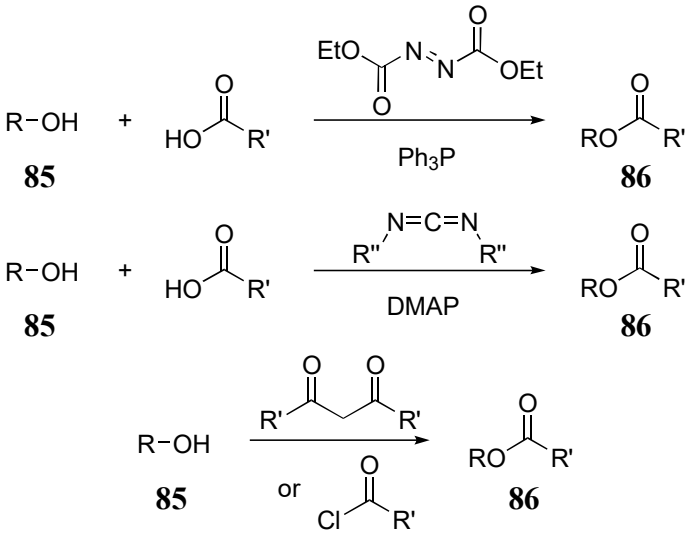
Scheme 3.6: Two mechanisms for the tosylation of alcohol **81**. Adapted from literature [34] [39]

Accodring to Salomon and Salomon, alcohols can be triflylated using trifluoromethanesulfonic anhydride and pyridine, via a similar mechanism as presented in scheme 3.6 [40]. However, mesylation does not transpire by this pathway. This is because mesyl chloride can be deprotonated by a base, thus leading to the formation of a sulfene intermediate, which is converted into a mesylate via nucleophilic attack and a subsequent intramolecular rearrangment [34]. The process is displayed in scheme 3.7.



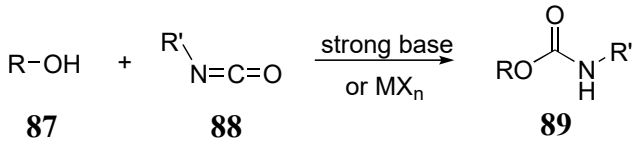
Scheme 3.7: NEt_3 -mediated mesylation of an alcohol. Adapted from literature [34]

The esterification of an alcohol would also be a viable way of enhancing the likelihood of successfully cleaving the C-O bond. There are numerous reported esterification methods, such as treating an alcohol with an acyl chloride or an acid anhydride [41], performing a Steglich esterification [42] or using a Mitsunobu reaction [43]. In the Steglich method, an alcohol and a carboxylic acid react with a carbodiimide under catalysis by 4-dimethylaminopyridine, whereas the Mitsunobu procedure requires triphenylphosphine and an azodicarboxylate in order to cause a reaction between an alcohol and a carboxylic acid. These processes are demonstrated in scheme 3.8.



Scheme 3.8: Methods for the esterification of alcohol **85**. Modified from literature [41] [42] [43]

Chaturvedi reported that alcohols can also be transformed to carbamates, by having the alcohols react with isocyanates [44]. It was also reported that strong bases and metal halides were the main facilitators of the reaction. The process is illustrated in scheme 3.9.



Scheme 3.9: Synthesis of carbamate **89** from alcohol **87** and isocyanate **88**. Modified from literature [44]

Based on the observed reports, it was decided to prepare monotosylated and monotriflylated derivatives of decane-1,2-diol, as the enhanced leaving group ability would be useful in the deoxygenation stage. Furthermore, it was decided to attempt three esterifications, based on the pathways displayed in scheme 3.8: the first one with trichloroacetyl chloride, the second with ethyl malonyl chloride and the third with monoethyl malonate, using the Steglich procedure. Not only would this give insight on whether the ester derivatives would be able to undergo deoxygenation with PCS, but it would also allow for the comparison of the different esterification methods and their respective nuances. Finally, the carbamation of decane-1,2-diol with phenyl isocyanate was attempted, because it was believed that the carbamate would really test the reductive capability of the PCS-Lewis base system.

4 Results and discussion

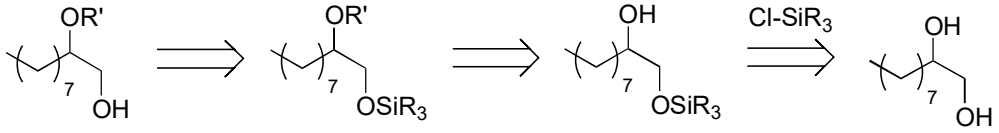
The goal of this chapter is to provide a brief overview of all the results that were collected during the thesis work project. The chapter is divided into two main sections: the first section describes the attempted derivatizations of decane-1,2-diol and the selective syntheses of various diol derivatives, while the second section is focused on the attempted deoxygenations of the prepared diol derivatives.

The experimental work was carried out at Tampere University of Technology, in the synthesis laboratory of the Laboratory of Chemistry and Bioengineering, between September 2017 and April 2018. A more in-depth description of the experimental methods that were used during the thesis work project is presented in chapter 6.

4.1 Preparation of decane-1,2-diol derivatives

As the main focus of the experimental work was on deoxygenating secondary derivatives of decane-1,2-diol **62**, it was necessary to ensure that the functionalizations were performed in a selective fashion. The goal of achieving these selective molecular manipulations posed a challenge, as the secondary hydroxyl group is less reactive than the primary hydroxyl group, which means that the process of functionalizing the primary hydroxyl group is always naturally favored [45]. As a result, a plan had to be developed to ensure that the reactions would transpire as intended. Scheme 4.1 illustrates the planned synthetic pathway.

The idea was to first treat decane-1,2-diol **62** with a silyl chloride, so that a silyl group would attach to the primary hydroxyl group, turning it into a silyl ether and thus preventing any other reactions from taking place at that site. After the protection of the primary



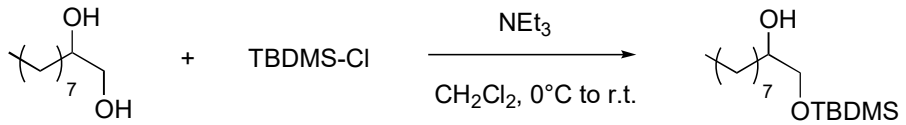
92 **91** **90** **62**

Scheme 4.1: Hypothesized pathway for the selective functionalization of the secondary hydroxyl group of decane-1,2-diol **62**.

hydroxyl group, the remaining hydroxyl group of **90** could freely be functionalized, to give **91**. To obtain the desired derivative **92**, the silyl group would be removed in a separate reaction, after the functionalization had been performed.

4.1.1 Selective TBDMS-monoprotection of decane-1,2-diol

For the purposes of this project, TBDMS was chosen as the silyl group for the hydroxyl group protection, as it provides relatively easy protection and deprotection reactions, along with good stability against a variety of reagents [46]. The protection reaction is displayed in scheme 4.2.



62 **93** **94** (77%)

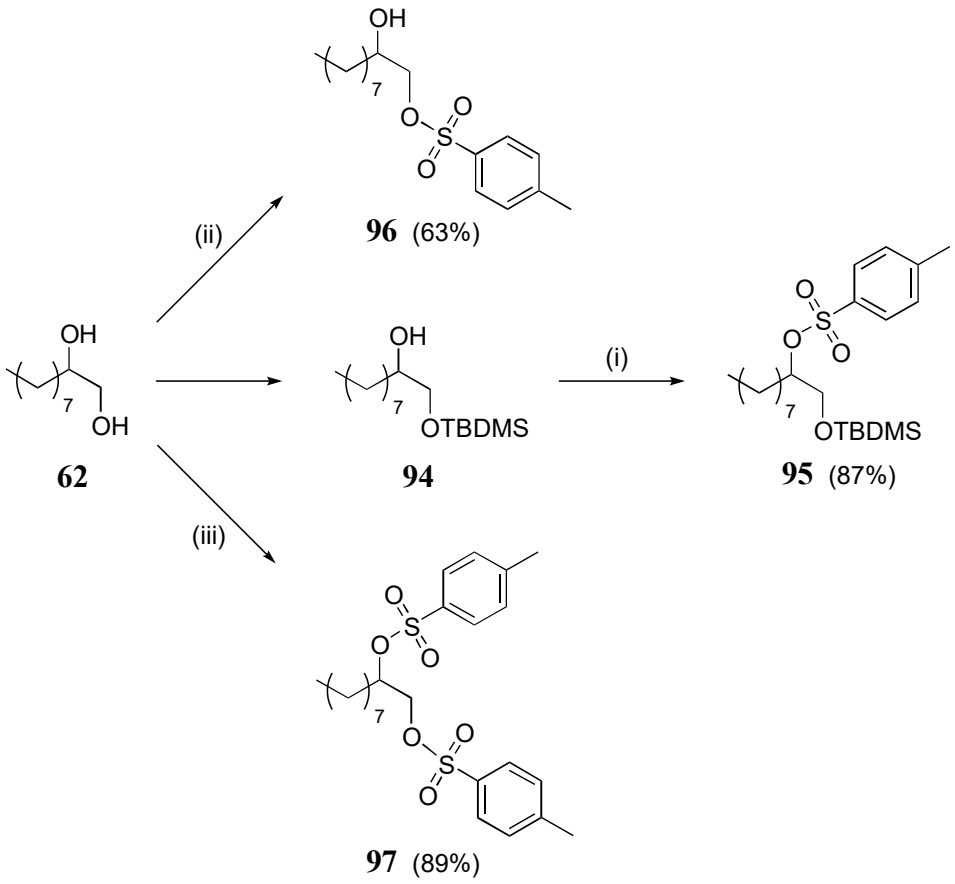
Scheme 4.2: Preparation of 1-((*tert*-butyldimethylsilyl)oxy)decan-2-ol **94**

In order to prevent the functionalization of the primary hydroxyl group in the following reactions, decane-1,2-diol **62** was treated with *tert*-butyldimethylsilyl (TBDMS) chloride **93** to give the corresponding silyl ether **94**. However, to avoid the possibility of the silylation of the secondary hydroxyl group via the formation of the bis-substituted diol, the reaction had to be performed in an excess of **62**.

The use of a silyl chloride usually leads to the formation of hydrochloric acid as a side product, which could lead to the unintended desilylation of **94** [46]. Therefore triethylamine was added into the mixture to ensure that any hydrochloric acid would immediately get neutralized by the strong base. Ultimately, the protection of **62** into **94** was a straightforward process, where **94** demonstrated to be stable towards column chromatography and was obtained in 77% yield.

4.1.2 Selective tosylations of decane-1,2-diol

Selective tosylations of the primary and secondary hydroxyl groups of decane-1,2-diol **62** were performed to prepare derivatives for the deoxygenation experiments, whereas the corresponding bistosylate was prepared as a part of a study on the biological activity of long-chain diol derivatives [32]. The methods for the preparation of tosylated derivatives of decane-1,2-diol are illustrated in scheme 4.3.



Scheme 4.3: Selective tosylations of decane-1,2-diol **62**. Reagents and conditions: (i) $CH_3C_6H_4SO_2Cl$ (2 Eq), DMAP (2 Eq), NEt_3 (4 Eq), CH_2Cl_2, 7 h, r.t.; (ii) $CH_3C_6H_4SO_2Cl$ (1.5 Eq), DMAP (8 mol%), NEt_3 (2.1 Eq), CH_2Cl_2, 23 h, r.t.; (iii) $CH_3C_6H_4SO_2Cl$ (3 Eq), DMAP (1 Eq), NEt_3 (4 Eq), CH_2Cl_2, 7 h, r.t.

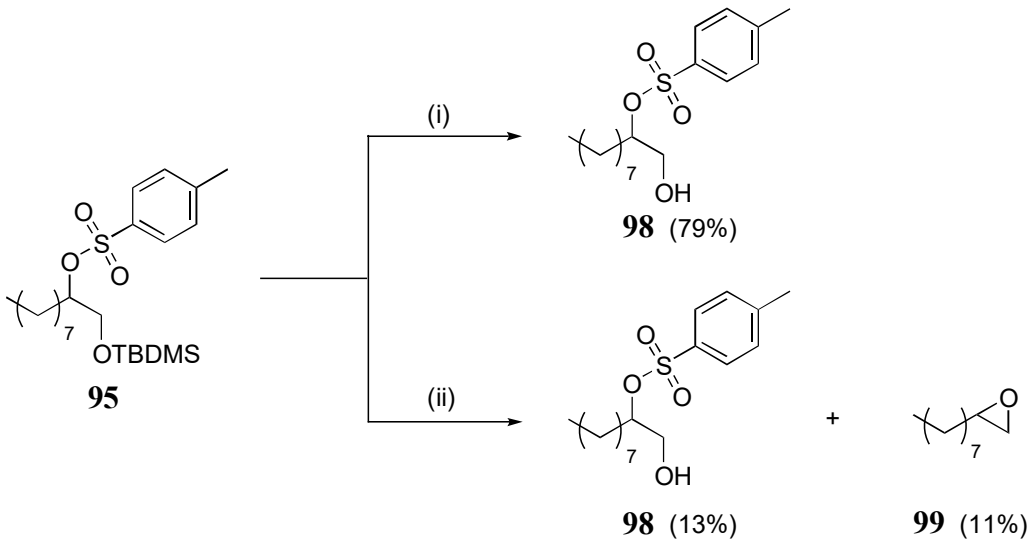
The tosylation of the secondary alcohol was carried out by treating the previously prepared compound **94** with tosyl chloride, using 4-dimethylaminopyridine as catalyst and triethylamine to trap any forming hydrochloric acid. The reaction worked very well and gave **95** in 87% yield.

The tosylation of the primary alcohol was performed with a similar procedure, although the amounts of reagents were adjusted. This reaction proved to be more challenging, as the reaction was carried out by using the unprotected decane-1,2-diol **62** as the starting material, which meant that there was no protecting group to prevent the formation of the bistosylate **97**. Regardless, the secondary alcohol **96** was obtained as the major product in 63% yield. Higher yields have been reported in literature, so it could be possible to further optimize the reaction [39].

The synthesis of the bistosylate **97** also had some initial challenges, as earlier attempts were quite slow and inefficient. However, by making adjustments to the amounts of reagents, the reaction performed very well and gave **97** in 89% yield.

The deprotection methods of **95** are described in scheme 4.4. Tetra-*n*-butylammonium fluoride was used in the first deprotection attempt, which resulted in a poor 13% yield of **98**. Along with the major product, the corresponding epoxide **99** was recovered in 11% yield. The formation of **99** indicates that, although TBAF is a suitable agent for the cleavage of the O-Si bond, it does not avoid the formation of the epoxide upon intramolecular nucleophilic substitution by the primary hydroxyl group to the vicinal secondary carbon. Other attempts were also made using the same method with different amounts of tetra-*n*-butylammonium fluoride, while keeping the reaction at 0 °C for the entire duration of the reaction. The reaction times were also kept as short as possible to limit the formation of **99**. Even though the yields somewhat increased during the following attempts, it was deemed that this procedure was not the best method of deprotecting **95**.

Ammonium fluoride was reported in literature as an alternative to tetra-*n*-butylammonium fluoride, so it was chosen as the deprotecting agent for the second attempt [47]. It was believed that as the fluoride ion would desilylate **95**, the ammonium ion would immediately protonate the desilylated intermediate and thus prevent the formation of **99**. The reaction with ammonium fluoride in methanol ended up being significantly slower than the previous attempts, but it also proved to be more selective. **98** was ultimately obtained in 79% yield, which is significantly higher than any reaction with tetra-*n*-butylammonium fluoride was able to produce.

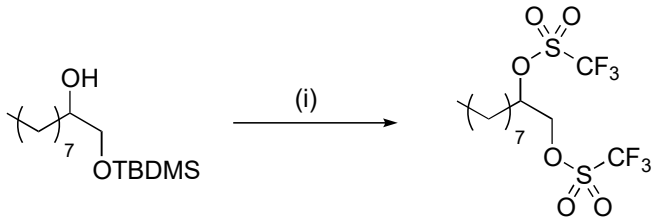


Scheme 4.4: Deprotection pathways of **95**. Reagents and conditions: (i) NH_4F, MeOH, 26 h, r.t.; (ii) TBAF, NH_4Cl, THF, 85 min, 0 °C to r.t.

4.1.3 Studies on the selective triflylation of decane-1,2-diol

For the purposes of the project, the goal was to only produce the secondary triflate. Therefore it was decided to start from the protected diol **94** and functionalize it into the TBDMS-protected intermediate, which could then be deprotected to obtain the desired triflylated derivative.

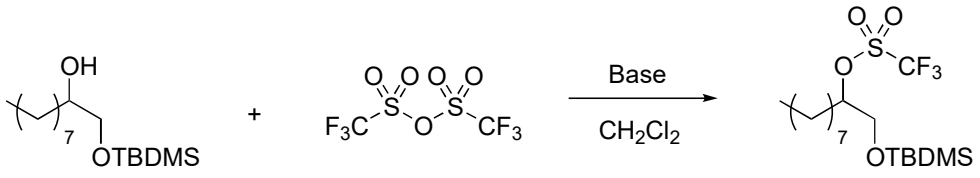
At first, a general procedure for the preparation of triflates was adapted from literature [40]. The TBDMS-protected diol **94** was treated with triflic anhydride **100** in the presence of pyridine, but the reaction did not behave as expected, as the formation of multiple products was observed on TLC. Ultimately, the corresponding bistriflate **101** was isolated as the major product in 39% yield, which is described in scheme 4.5.



94 **101** (39%)

Scheme 4.5: Unintended synthesis of **101**. Reagents and conditions: (i) $(CF_3SO_2)_2O$ (1 Eq), Pyridine (1 Eq), CH_2Cl_2, 18 h, 0 °C to r.t.;

The formation of **101** would suggest that the silyl protecting group is cleaved off during the process. Similar behaviour has been reported in literature for silyl protected alcohols, in reactions that use triflic anhydride **100** [48]. It was therefore decided to increase the amount of base in an effort to prevent the unintentional desilylation of **94**. Furthermore, as **94** was previously added into triflic anhydride **100**, it was decided that the addition order should be reversed, as it was believed that this would reduce the likelihood of the silyl group cleaving off. Finally, it was also decided that the reaction time should be drastically reduced, and that the reaction mixture should be kept at 0 °C for the entire duration of the reaction. A general plan for the reaction is presented in scheme 4.6.



94 **100** **102**

Scheme 4.6: Plan for the attempted triflylation of **94**

A second attempt was made using the previously described method, but that didn't offer the desired result either, as the reaction afforded a mixture of products, none of which were isolable by column chromatography. It was then believed that the protecting group had cleaved off again, which would explain the result of obtaining a mixture of many compounds. The same reaction was then repeated, with the exception of replacing pyridine with triethylamine, which is a much stronger base. This time, a mixture of many compounds was obtained after column chromatography in a relatively low yield, although it was observed on NMR that the silyl group was not present in the mixture. It was then concluded that this method of triflylation was completely unsuitable to perform the intended manipulations, and that an alternative approach had to be taken.

A method for the triflylation of *tert*-butyldiphenyl silyl protected 1,2-diols was reported in literature and was adapted for the purposes of this thesis work [49]. In the new method, the reaction temperature was lowered from 0 °C to -10 °C and the equivalents of reagents were increased. However, the amount of solvent was also increased so that the concentration of the reaction was significantly lower. In addition, the post-reaction work-up was also performed at 0 °C. The addition order was not changed.

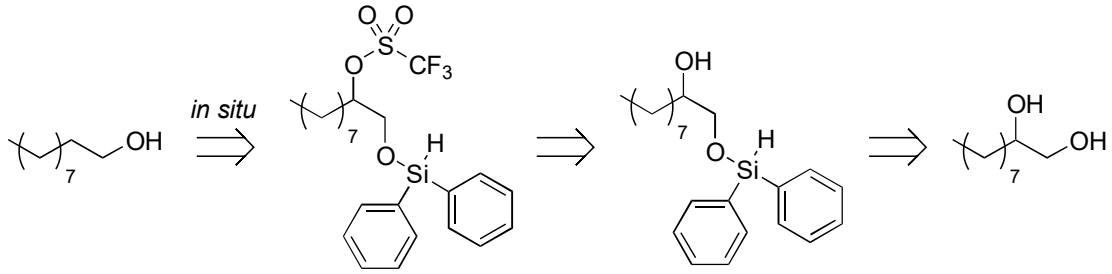
The first attempt looked interesting on TLC, but right before the reaction reached the point of complete consumption of the starting material **94**, it appeared on TLC as if the formed products had decomposed. Column chromatography was performed to the reaction mixture, but no products were isolable. The reaction was then repeated with more reagents to make it faster, and while no significant decomposition was observed on TLC, purification by column chromatography resulted in a mixture of multiple compounds in a low yield. As the starting material had not been entirely consumed during the reaction, another attempt was made with the same major parameters, with the exception of increasing the duration of the reaction. However, as this also resulted in a mixture of compounds in a low yield, it was decided to look for other options. The summary of the reactions is presented in table 4.1.

Table 4.1: Attempted triflylations of **94**

Entry	**100** (eq)	Base (eq)	CH_2Cl_2 (mL)	T (°C)	Time (min)	Result
1	1	Pyridine (2)	1	0	40	No product
2	1	NEt_3 (2)	1	0	25	Mixture
3	2	Pyridine (4)	10	-10	35	No product
4	3.1	Pyridine (5)	10	-10	25	Mixture
5	3.1	Pyridine (5)	10	-10	90	Mixture

In an effort to explore another possible pathway to preparing **102**, **94** was treated with triflic chloride in dichloromethane at 0 °C, using 4-dimethylaminopyridine as catalyst and triethylamine to trap hydrochloric acid. This procedure did not produce the desired result either, as the reaction afforded a moderate yield of a product that could not be characterized.

After some considerations, an alternative strategy was developed. As the efforts to prepare and isolate **102** proved unsuccessful, it was decided to move on to a more straightforward approach. The idea was to attach a silane into the primary hydroxyl group of decane-1,2-diol **62**, after which the secondary hydroxyl group would be triflylated. This way, the triflate would make for a good leaving group, which would increase the probability of hydride delivery from the silane, thus increasing the possibility of an *in situ* deoxygenation. The idea is illustrated in scheme 4.7.



Scheme 4.7: Retrosynthetic plan for the selective triflylation and the following *in situ* deoxygenation

At first, in order to produce **103**, decane-1,2-diol was treated with diphenylchlorosilane in dichloromethane at -78 °C, while using triethylamine to trap any forming hydrochloric acid. The reaction afforded a mixture of different products, which was then subjected to column chromatography for purification. However, the NMR spectra taken before and after the purification suggested that the products decomposed during the process, showing the unstable nature of the species formed. Hence, a different strategy devoided of an extensive purification of the reaction mixture was envisioned.

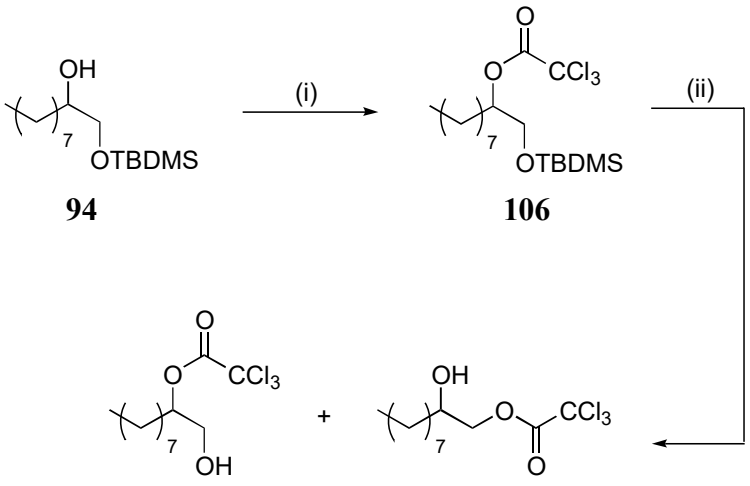
As the idea of exposing the products to an aqueous work-up was not deemed suitable, the filtration of the salt of triethylamine and hydrochloric acid remained the only method of purification for this reaction. After a careful consideration, it was decided that the filtration would not be performed, as it seemed unnecessary. Furthermore, the option of not stopping the reaction for filtration offered the advantage of keeping it under argon at all times, thus reducing the probability of exposing any formed products to air-based moisture.

Another similar reaction was then run, but this time trific anhydride **100** and pyridine were added directly into the reaction, as the temperature was elevated to -10 °C. Tetra-*n*-butylammonium fluoride was added later at 0 °C in similar fashion. Purification by column chromatography yielded mixtures of compounds, none of which contained the desired product. NMR analysis of the crude mixture revealed mostly decane-1,2-diol **62**, and the desired deoxygenation products could not be identified.

Impelled by the described lack of stability of the triflylated derivative of decane-1,2-diol, its use as a precursor for the deoxygenation was abandoned.

4.1.4 Selective acylations of decane-1,2-diol

Using the plan that was presented in scheme 4.1, it was decided to acylate the secondary hydroxyl group of decane-1,2-diol **62** in two ways. The first functionalization was performed by treating the TBDMS-protected intermediate **94** with trichloroacetyl chloride in diethyl ether at 0 °C, using triethylamine to neutralize any forming hydrochloric acid. The reaction is illustrated in scheme 4.8.



Scheme 4.8: Preparation of esters **107a** and **107b**. Reagents and conditions: (i) $ClCOCCl_3$, NEt_3, Et_2O, 25 min, 0 °C, 90% yield; (ii) HCl, Et_2O, 66 h, r.t., combined yield 63%, ratio of products (1:1)

Using the aforementioned method, the acylated product **106** was easily obtained after a fast reaction without further purification, aside from a brief aqueous work-up. The yield of the reaction was 90%, which indicates that the reaction performed extremely well.

The next step was to move on to the deprotection of **106**, as described in scheme 4.8. The first attempts, performed using tetra-*n*-butylammonium fluoride in tetrahydrofuran and ammonium fluoride in methanol, did not prove to be successful. Instead of affording the desired result, the reactions gave mixtures of compounds in low yields.

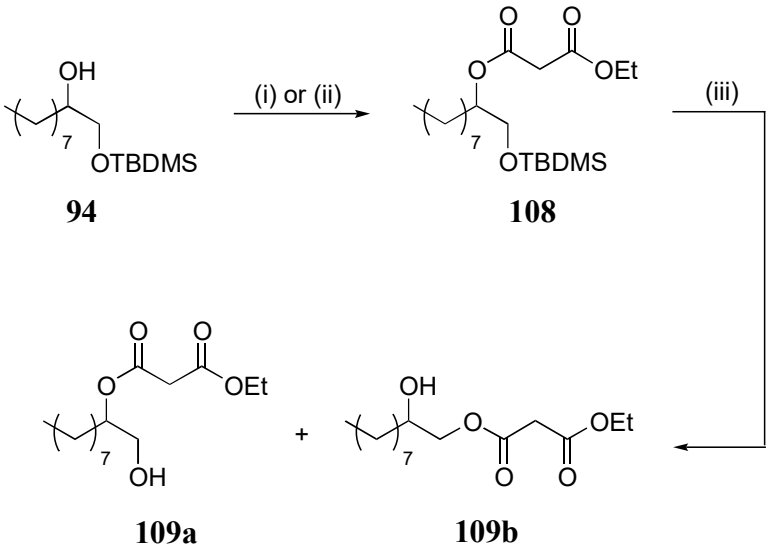
An alternative strategy was then deployed, as **106** was treated with a solution of hydrochloric acid in dry diethyl ether at room temperature. While the deprotection with hydrochloric acid did perform the intended desilylation of **106**, it also unexpectedly resulted in the formation of the mixture of regioisomers **107a** and **107b** in a 1:1 ratio in 63% yield. The formation of these products can be explained by an acid-catalyzed intramolecular transesterification upon desilylation.

Attempts to purify and separate the two compounds by column chromatography were to no avail. After some considerations, it was decided that the mixture of **107a** and **107b** would be used as is in the following reactions, as it was hypothesized that the simultaneous presence of the two regioisomers would provide additional information about the nature of the C-O bond required for the intended deoxygenation.

Another acylated derivative of decane-1,2-diol, **108**, was then prepared in two ways, as illustrated in scheme 4.9. The first attempt was performed via Steglich-esterification, by treating **94** with monoethyl malonate in dichloromethane at room temperature, using *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride and 4-dimethylaminopyridine as base [42]. Despite the high selectivity determined by TLC, as only the desired product was observed, the low conversions and rates required addition of superstoichiometric amounts of reagents to increase the conversion. Ultimately, the acylated product **108** was obtained in 55% yield.

As an alternative approach, **94** was treated with ethyl malonyl chloride in diethyl ether, using triethylamine to trap any formed hydrochloric acid, in a similar procedure than what was performed to prepare **106**. This reaction was much faster than the previous attempt, while also showing similar selectivity. However, the reaction also suffered from the same problem as the Steglich-esterification, which was the requirement for the addition of more reagents to push the reaction to completion. Despite the similar yield obtained with this method (64%), it was chosen for further experiments due to its shorter reaction time.

108 was deprotected with tetra-*n*-butylammonium fluoride in tetrahydrofuran. Again, the compound was desilylated successfully, but the result ended up being a mixture of regioisomers **109a** and **109b** in 71% yield, in a ratio of 5:8.



94 **108** **109a** **109b**

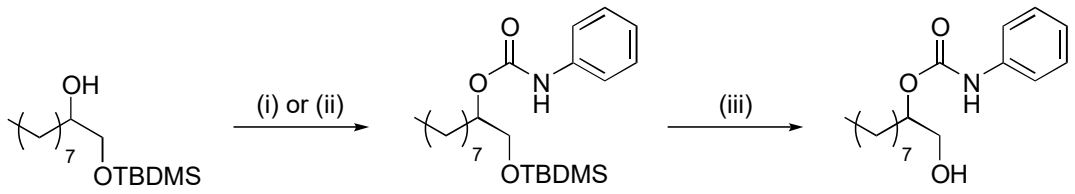
Scheme 4.9: Preparation of esters **109a** and **109b**. Reagents and conditions: (i) $HOCOCH_2COOEt$, EDC·HCl, DMAP, CH_2Cl_2, 5h, r.t., 55% yield; (ii) $ClCOCH_2COOEt$, NEt_3, Et_2O, 2.5 h, 0 °C to r.t., 64% yield; (iii) TBAF, NH_4Cl, THF, 2 h, 0 °C to r.t., combined yield 71%, ratio of products (5:8)

As the same problem had already been encountered during the process of deprotecting **106**, it was decided that the mixture of regioisomers would not be purified by column chromatography. Instead, the mixture of **109a** and **109b** was used as is in the deoxygenation studies.

4.1.5 Selective carbamation of decane-1,2-diol

The secondary hydroxyl group of decane-1,2-diol **62** was carbamated according to the pathway presented in scheme 4.1. As it was reported in literature that such manipulations between alcohols and isocyanates could be performed by using strong bases [44], **94** was treated with phenyl isocyanate in dichloromethane in the presence of triethylamine, as presented in scheme 4.10. The intermediate **110** was obtained in 42% yield after a slow reaction, where reagents had to be added multiple times to increase the conversion to products. The result suggested that a better alternative would have to be developed.

The reaction was then repeated, with the exception of increasing basicity by replacing triethylamine with 1,8-diazabicyclo[5.4.0]undec-7-ene, and also increasing the amounts of reagents that were used. The reaction was significantly faster this time and progressed to completion at ease, affording **110** in 79% yield.



94 **110** **111**

Scheme 4.10: Preparation of **111**. Reagents and conditions: (i) PhNCO, NEt_3, CH_2Cl_2, 47 h, r.t., 42% yield (ii) PhNCO, DBU, CH_2Cl_2, 14 h, r.t., 79% yield; (iii) TBAF, NH_4Cl, THF, 90 min, 0 °C to r.t., 89% yield

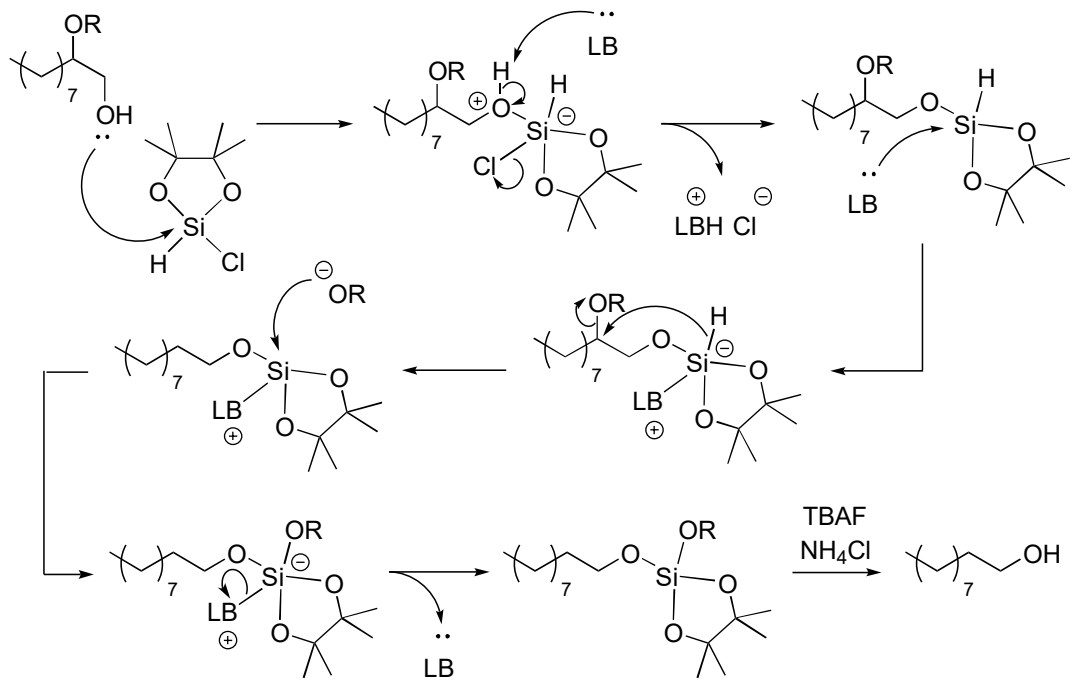
110 was then deprotected with tetra-*n*-butylammonium fluoride in tetrahydrofuran, as illustrated in scheme 4.10. **111** was obtained in 89% yield after purification by column chromatography.

4.2 Experiments with PCS

The decane-1,2-diol **62** derivatives were then subjected to a number of tests with PCS, to observe the viability of the selective deoxygenations. The idea was to first perform a series of small scale experiments, which would be analyzed by TLC to observe the development of the reactions. Whenever new compounds were formed, the corresponding reactions would then be scaled up, to obtain a reasonable amount of isolable product for characterization. This would also act as a secondary measure of confirming the TLC-based results, as it would allow the opportunity of testing the reproducibility of the experiments.

A proposed mechanism for the Lewis base mediated PCS-deoxygenation of secondary decane-1,2-diol derivatives **62** into 1-decanol is illustrated in scheme 4.11. A similar mechanism can also be proposed for primary decane-1,2-diol **62** derivatives, with the exception of having 2-decanol as the expected product.

The main principle behind the mechanism is the suggested dual functionality of Lewis bases, which would act as a catalyst for hydride delivery, and also as a neutralizing agent for any forming hydrochloric acid, in order to prevent unintentional desilylation. The compounds would be desilylated after the intended reactions had been performed, using tetra-*n*-butylammonium fluoride in tetrahydrofuran.



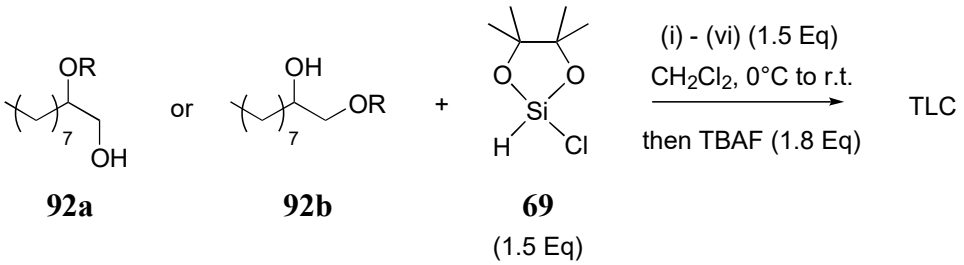
Scheme 4.11: Hypothetical mechanism for the Lewis base (LB) catalyzed deoxygenation of a decane-1,2-diol derivative with PCS

4.2.1 TLC-monitored reactions

The initial PCS-experiments were performed in a scale of 20 mg diol derivative per reaction, as the goal was to only analyze the reaction mixtures on TLC, during the various stages of the process. Efforts were made to keep various reaction parameters, including the equivalents of reagents, the reaction temperatures and the reaction times, as constant as possible. That way, the effects of random factors into the results of the reactions were minimized.

As the role of the Lewis base is so crucial in the proposed reaction mechanism, it was also decided to test several bases with different properties, to see the effect they would have on the reaction. The bases that were chosen for the experiments were *N*-diisopropylethylamine, pyridine, imidazole, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine-*N*-oxide and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. These bases were chosen, as they offer different basic strengths, nucleophilicities and functionalities, while also providing a metal-free, organocatalytic approach to the process. The same bases were also previously screened and found suitable for the activation of PCS in the reduction of salicylaldehydes [7].

A general procedure of the PCS-experiments for decane-1,2-diol derivatives is presented in scheme 4.12. Derivative **92a** or **92b** was treated with PCS **69** in six simultaneous reactions in dichloromethane at 0 °C, using one of the aforementioned bases in each reaction.



92a **92b** **69** (1.5 Eq)

Scheme 4.12: General process of testing derivatives **92a** and **92b** in PCS-reactions. Reagents and conditions: (i) DIPEA; (ii) Pyridine; (iii) Imidazole; (iv) DBU; (v) Pyridine-*N*-oxide; (vi) DMPU

It was decided beforehand that the total time of the process should be around 24 hours, so that the reactions were given enough time to form new products. Additionally, the reaction time could be used as a standard when comparing the rates and efficiencies of different reactions. After stirring at room temperature for at least 20 hours, each reaction was treated with tetra-*n*-butylammonium fluoride, after which they were quenched with ammonium chloride.

The reactions were monitored simultaneously via TLC during specific intervals, to get an idea of their developments over the course of the whole process. Any products that were formed were compared on TLC to 1-decanol and 2-decanol standard solutions, which were prepared from commercially available reagents. After the final analysis, which was performed after the reactions were quenched, decisions were made on how and if the experiments should be continued. The results of the TLC-experiments are presented in figure 4.1.

The spots that formed on TLC and the reaction rates were used as criteria, when choosing reactions for the up-scaling phase. Only the spots that were defined well enough were chosen for further investigations, whereas the spots that were very small or faint on TLC were ignored, because it was deemed that such products could not be isolated in reasonable quantities. PCS-related TLC-spots were also ignored, as PCS **69** gave a characteristic pinacol spot right above the application point. Any application point spots were also not taken into account.

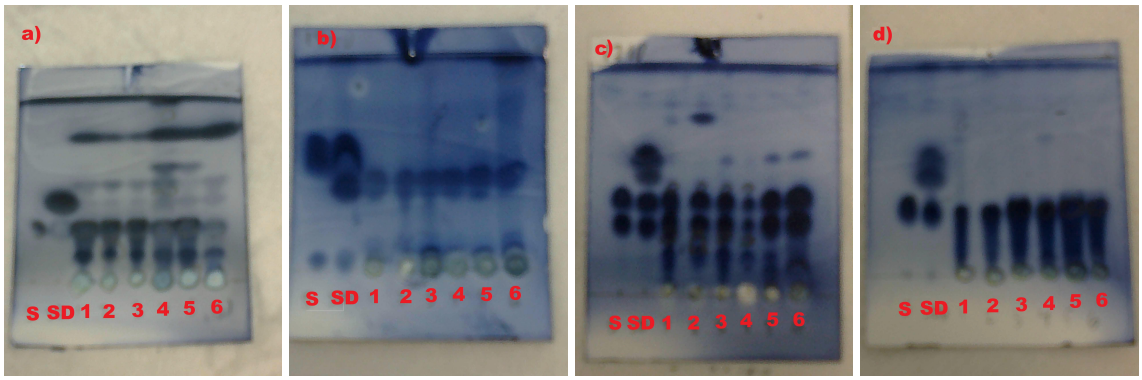


Figure 4.1: Results for the TLC-experiments of a) **98**; b) **107a**:**107b** (1:1 ratio); c) **109a**:**109b** (5:8 ratio); and d) **111**. Abbreviations: S = starting material, SD = co-spot with starting material and the expected products, 1-6 = reaction mixtures (i) - (vi) from scheme 4.12.

For compound **98**, reactions (iv) and (vi) were selected to be repeated. Reaction (iv) looked quite active, as it afforded a number of new products on TLC. On the other hand, reaction (vi) gave one strong spot, thus indicating significant selectivity. Both reactions also showed signs of significant consumption of the starting material, in comparison to the other reactions.

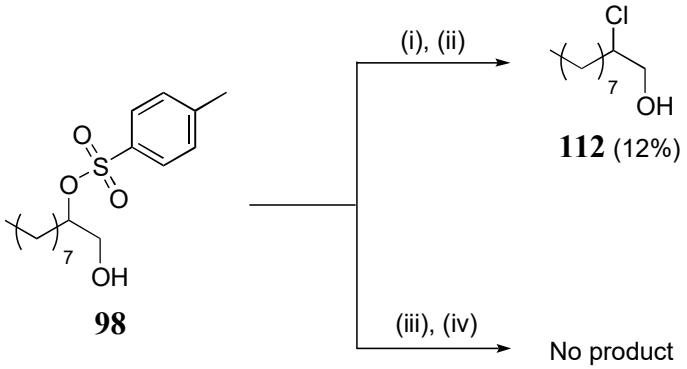
The reactions of the mixture of **107a** and **107b** turned out to be the most reactive, as all six reactions completely consumed the starting material. All of the reactions produced only one spot, which exhibited the same retardation factor as one of the expected products. Even though all the reactions led to the same result, reaction (iv) was chosen to be scaled up, as it proved to be the fastest reaction.

For the mixture of **109a** and **109b**, reactions (ii) and (vi) were chosen to be repeated, even though the consumption of the starting material was not that significant based on TLC analysis. Reaction (ii) produced a unique spot, which was not observed in any of the other reactions. Reactions (iii)-(vi) produced a spot, which had a similar retardation factor as one of the expected products. Because the spot was most prominent in reaction (vi), it was selected for the upscaling.

For compound **111**, no significant product formation was observed during any of the reactions. Therefore it was decided that none of them would be repeated.

4.2.2 Upscaled PCS-reactions

The reactions that were chosen for further investigations were then repeated, using a scale of 50 mg of diol derivative as the standard amount, as the goal was to isolate and characterize any formed products that were of interest. The upscaled PCS-reactions of **98** are presented in scheme 4.13.

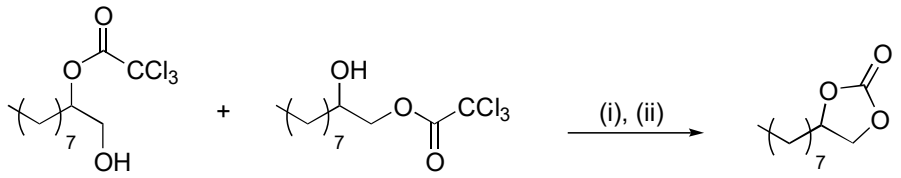


Scheme 4.13: PCS-reaction of **98**. Reagents and conditions: (i) PCS, DBU, CH_2Cl_2, 50 h, 0 °C to r.t.; (ii) TBAF, NH_4Cl, CH_2Cl_2, 20 min, r.t.; (iii) PCS, DMPU, CH_2Cl_2, 27 h, 0 °C to r.t.; (iv) TBAF, NH_4Cl, CH_2Cl_2, 40 min, r.t.

Unfortunately, the deoxygenation of **98** into 1-decanol was not observed. Instead, the reaction of **98** with PCS **69** and 1,8-diazabicyclo[5.4.0]undec-7-ene afforded the halogen-substituted compound **112** in 12% yield. The reaction with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone did not afford any major product, as instead some very small spots were observed on TLC, which then led to the decision of forgoing their isolation.

Even though no small scale experiments were conducted for derivative **96**, it was decided to perform an upscaled reaction with **96**, PCS **69** and 1,8-diazabicyclo[5.4.0]undec-7-ene, based on the results that were observed during the experiments for the secondary tosylate **98**. The formation of 2-decanol was not observed, and as only a few small spots were observed on TLC, no products were isolated from the experiment.

The mixture of **107a** and **107b** was treated with PCS **69** in similar fashion, using 1,8-diazabicyclo[5.4.0]undec-7-ene as the base. The reaction progressed rapidly to the point of complete consumption of the starting material, exhibiting the formation of a new single product, even though a mixture of regioisomers was used as starting material. The new product that was formed was stable to treatment with tetra-*n*-butylammonium fluoride and was obtained in 80% yield after isolation. Its structure was elucidated to be the cyclic carbonate **113**. The result of the experiment is illustrated in scheme 4.14.

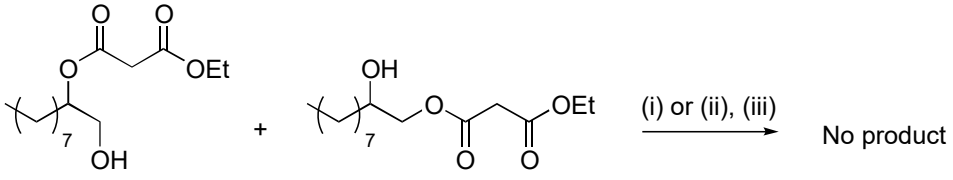


107a **107b** **113** (80%)

Scheme 4.14: PCS-reaction for the mixture of **107a** and **107b**. Reagents and conditions: (i) PCS, DBU, CH_2Cl_2, 4 h, 0 °C to r.t.; (ii) TBAF, NH_4Cl, CH_2Cl_2, 30 min, r.t.

As similar results had been reported in literature, in reactions that did not use PCS **69**, it was then deduced that the compounds **107a** and **107b** could not be deoxygenated with this method [50]. It became clear that PCS **69** could not deliver the hydride in the intended fashion, as based on TLC analysis, all of the small-scale experiments led to the same result.

For the mixture of **109a** and **109b**, reactions with pyridine and 1,3-dimethyl-3,4,5,6--tetrahydro-2(1H)-pyrimidinone were repeated. Again, the formation of 1-decanol or 2-decanol was not observed, and unlike in the small scale experiments, no product formation was observed on TLC this time. The reaction seemingly proceeded in a similar fashion based on TLC observations, but the small spots that were formed during the reaction disappeared after the reactions were quenched with ammonium chloride. The experiments of **109a** and **109b** are illustrated in scheme 4.15.



109a **109b**

Scheme 4.15: PCS-reaction for the mixture of **109a** and **109b**. Reagents and conditions: (i) PCS, Pyridine, CH_2Cl_2, 23 h, 0 °C to r.t.; (ii) PCS, DMPU, CH_2Cl_2, 23 h, 0 °C to r.t.; (iii) TBAF, NH_4Cl, CH_2Cl_2, 1 h, r.t.

5 Conclusions

In an attempt to reduce the dependency on fossil fuels, the conversion of lignocellulosic biomass has been researched in the recent years. As the efficient deoxygenation of polyols could enable the production of sustainable fuels, polymers and chemicals, it continues to be a lucrative goal in the field of organic synthesis. Because of these goals, it was decided to research the selective deoxygenation of secondary vicinal diol derivatives.

Decane-1,2-diol was chosen as the starting material, which was then derivatized in in various ways. Most of the compounds were obtained without any problems, but some difficulties were also encountered. For example, the triflylated intermediate was never successfully isolated, despite numerous efforts and different methods, due to non-selective reactions and the difficulties in the purification of the obtained products. Furthermore, during the deprotections of intermediates **106** and **108**, the unexpected formation of two main products was observed. It was then decided to use the mixtures of products as a starting material for the deoxygenation studies, as the separation of the products via column chromatography proved challenging.

Using the PCS-Lewis base procedure developed by Assoah *et al.* [7], the derivatives were experimented on, in an attempt to develop a novel two-step method for the selective deoxygenation of vicinal diols. The experiments were at first carried out in small scale to perform TLC-analyses, after which the reactions were scaled up based on the results displayed on TLC. While some new products were obtained from the PCS-experiments, the intended deoxygenations were unfortunately not observed. Even though the reducing capabilities of the PCS-Lewis base system could not be applied to the decane-1,2-diol derivatives during the course of this project, the possibility of deoxygenation for vicinal diol derivatives with PCS can not be ruled out with complete certainty. For example, adjustments could be made to various reaction parameters, or entirely new substrates could be prepared. The experiments could also be repeated, using a different starting material.

It was also mentioned in section 2.2.3 that the combination of $B(C_6F_5)_3$ and a hydrosilane has also been identified as a potent reductive system. In the light of the results that were obtained during the course of this thesis work, it would be interesting to see whether the decane-1,2-diol derivatives could instead be deoxygenated with other hydrosilanes, possibly by using $B(C_6F_5)_3$ as catalyst. Furthermore, as the PCS-experiment for the mixture of **107a** and **107b** led to the formation of **113**, it would also be interesting to attempt the hydrosilane-induced ring opening of **113**. Additional research is required on the subject.

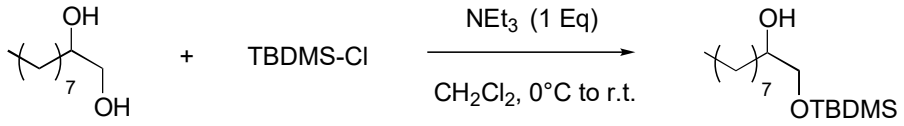
6 Experimental methods

6.1 General remarks

The progress of all reactions was monitored via thin-layer chromatography, using commercially available Merck 60 F254 silica gel plates. The plates were examined under a 254 nm UV-light and stained with either cerium ammonium molybdate or potassium permanganate. Silica gel column chromatography, using silica gel 60 with a particle size of 40-63 μm, was used to purify the prepared products. NMR spectra were measured with a Varian Mercury spectrometer, using $CDCl_3$ as the solvent. ^{1}H NMR spectra were measured at a frequency of 300 MHz, ^{13}C NMR spectra were measured at a frequency of 75 MHz and ^{19}F NMR spectra were measured at a frequency of 282 MHz. The chemical shifts are indicated with δ and are reported in parts-per-million (ppm), whereas the coupling constants are indicated with *J* and are reported in hertz (Hz). The following abbreviations were used to report the peak splitting patterns in the NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, qd = quartet of doublets, m = multiplet. Waters ESI-TOF MS spectrometer was used to measure the high-resolution mass spectra. Anhydrous dichloromethane, tetrahydrofuran, diethyl ether and triethylamine were obtained using an Inert PureSolv PS-Micro solvent purification system. The anhydrous bases were obtained either via distillation or by using commercially available reagents.

6.2 Preparation of decane-1,2-diol derivatives

6.2.1 1-((*tert*-butyldimethylsilyl)oxy)decan-2-ol (94)

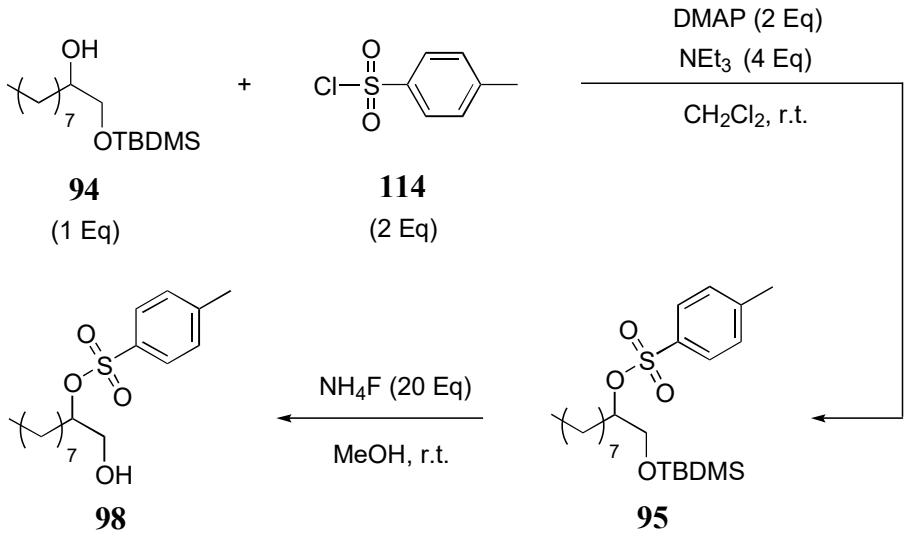


62 (1.2 Eq) **93** (1 Eq) **94**

Scheme 6.1: Synthesis of 1-((*tert*-butyldimethylsilyl)oxy)decan-2-ol **94**

To a stirred solution of decane-1,2-diol **62** (4.18 g, 24 mmol) in anhydrous dichloromethane (40 mL) at room temperature under argon, dry triethylamine (2.8 mL, 20 mmol) was added. The resulting mixture was cooled to 0 °C and a solution of tert-butyldimethylsilyl chloride **93** (3.02 g, 20 mmol) in anhydrous dichloromethane (20 mL) was added dropwise. After stirring at room temperature for 48 h, water (50 mL) was added and the aqueous layer was extracted with dichloromethane (2 x 80 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Silica gel column chromatography with *n*-hexane/EtOAc (97:3) afforded **94** (4.43 g, 77%, two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64-3.59 (m, 2H), 3.41-3.34 (m, 1H), 2.42 (d, J = 3.2 Hz, 1H), 1.41-1.27 (m, 14H), 0.91-0.85 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.0, 67.4, 32.9, 32.0, 29.9, 29.7, 29.4, 26.0, 25.7, 22.8, 18.4, 14.3.

6.2.2 2-(*p*-toluenesulfonyl)decan-1-ol (98)



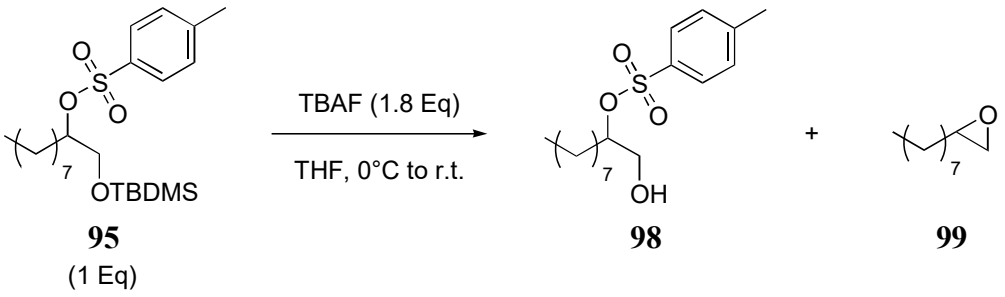
Scheme 6.2: Synthesis of 2-(*p*-toluenesulfonyl)decan-1-ol **98**

To a stirred solution of **94** (577 g, 2 mmol) in anhydrous dichloromethane (12 mL) at room temperature under argon, dry triethylamine (1.1 mL, 8 mmol), 4-dimethylaminopyridine (489 mg, 4 mmol) and *p*-toluenesulfonyl chloride **114** (763 mg, 4 mmol) were added. The reaction was stirred at room temperature for 7 h, after which the reaction was treated with saturated ammonium chloride solution (12 mL). The aqueous layer was extracted with dichloromethane (3 x 12 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by silica gel column chromatography with *n*-hexane/toluene (1:9) afforded **95** (769 mg, 87%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 4.51-4.44 (m, 1H), 3.71-3.60 (m, 2H), 2.43 (s, 3H), 1.71-1.54 (m, 2H), 1.30-1.17 (m, 12H), 0.91-0.84 (m, 12H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 134.6, 129.8, 128.0, 83.5, 64.2, 32.0, 31.2, 29.5, 29.4, 29.3, 25.9, 24.8, 22.8, 21.8, 18.4, 14.3.

To a stirred solution of **95** (734 mg, 1.7 mmol) in reagent quality methanol (20 mL) at room temperature under argon, ammonium fluoride (1.2 g, 33 mmol) was added. The mixture was stirred at room temperature for 26 h, after which the solvent was completely evaporated. Dichloromethane (10 mL), saturated ammonium chloride solution (10 mL) and a few drops of water were added to the crude mixture. The aqueous layer was extracted with dichloromethane (3 x 10 mL), after which the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography with *n*-hexane/EtOAc (3:1) to yield **98** (427 mg, 79%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 4.60-4.53 (m, 1H), 3.74-3.62 (m, 2H), 2.43 (s, 3 H), 2.25 (d, J = 4.1 Hz, 1H), 1.63-1.53 (m, 2H), 1.27-1.14 (m, 12H), 0.86 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 133.9, 129.9, 128.0, 84.8, 64.5, 31.9, 31.0, 29.4, 29.2, 29.2, 24.9, 22.7, 21.7, 14.2.

6.2.3 2-(*p*-toluenesulfonyl)decan-1-ol (98) and 2-octyloxirane (99)

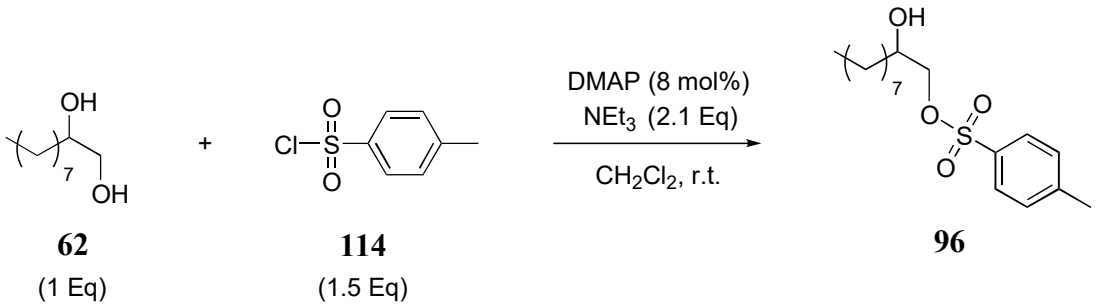


Scheme 6.3: Synthesis of 2-(*p*-toluenesulfonyl)decan-1-ol (**98**) and 2-octyloxirane (**99**)

To a stirred solution of **95** (367 mg, 0.83 mmol) in anhydrous tetrahydrofuran (1.5 mL) at 0 °C under argon, dry tetra-*n*-butylammonium fluoride solution (1.5 mL, 1 M tetrahydrofuran) was added dropwise. The reaction was stirred at 0 °C for 15 min, warmed up to room temperature and stirred for another 70 minutes. The mixture was quenched with saturated ammonium chloride solution (1.5 mL) and a few drops of water. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), after which the combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was

purified by silica gel column chromatography in two phases, first with *n*-hexane/ethyl acetate (98:2) and then with *n*-hexane/ethyl acetate (3:1), to separately obtain **98** (36 mg, 13%) and **99** (15 mg, 11%). In appearance, **98** was a yellow oil, whereas **99** was a colorless oil. **98** was obtained with similar spectral characterization as previously presented in section 6.2.2. **99** was obtained with similar spectral characterization as reported in literature [51]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.93-2.88 (m, 1H), 2.74 (dd, J = 4.0, 5.1 Hz, 1H), 2.46 (dd, J = 2.6, 5.0 Hz, 1H), 1.56-1.41 (m, 2H), 1.35-1.27 (m, 12H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.6, 47.3, 32.7, 32.0, 29.7, 29.6, 29.4, 26.1, 22.8, 14.3.

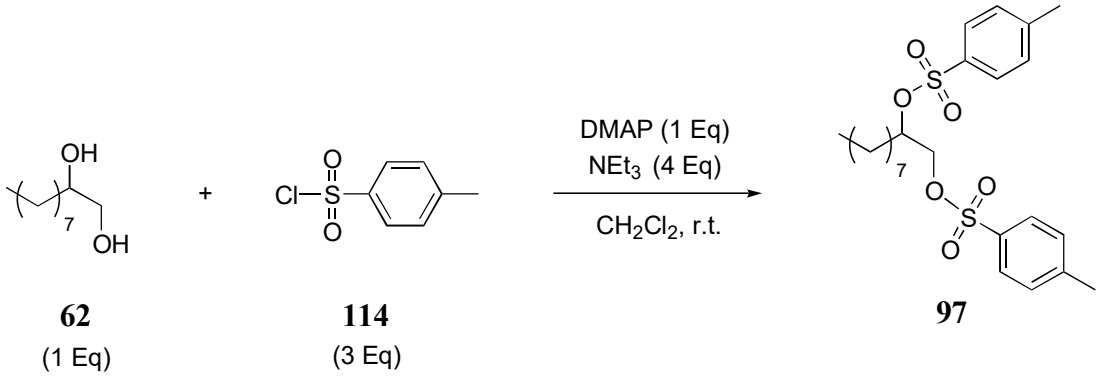
6.2.4 1-(*p*-toluenesulfonyl)decan-2-ol (96)



Scheme 6.4: Synthesis of 1-(*p*-toluenesulfonyl)decan-2-ol **96**

The procedure was adapted from literature [39]. To a stirred solution of decane-1,2-diol **62** (405 mg, 2.3 mmol) in anhydrous dichloromethane (23 mL) at room temperature under argon, dry triethylamine (0.67 mL, 4.8 mmol), 4-dimethylaminopyridine (22 mg, 0.2 mmol) and *p*-toluenesulfonyl chloride **114** (659 mg, 3.5 mmol) were added. The reaction was stirred at room temperature for 23 h, after which the mixture was diluted with diethyl ether (50 mL). Water (75 mL) was added and the organic layer was extracted, washed with brine (75 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with toluene/EtOAc (95:5) to yield **96** (478 mg, 63%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.05-4.01 (m, 1H), 3.90-3.85 (m, 2H), 2.44 (s, 4H), 2.12 (s, 1H), 1.40-1.39 (m, 4H), 1.31-1.24 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 132.8, 130.1, 128.1, 74.1, 69.6, 32.8, 31.9, 29.6, 29.5, 29.3, 25.3, 22.8, 21.8, 14.2.

6.2.5 Decane-1,2-diyl bis-(*p*-toluenesulfonate) (97)

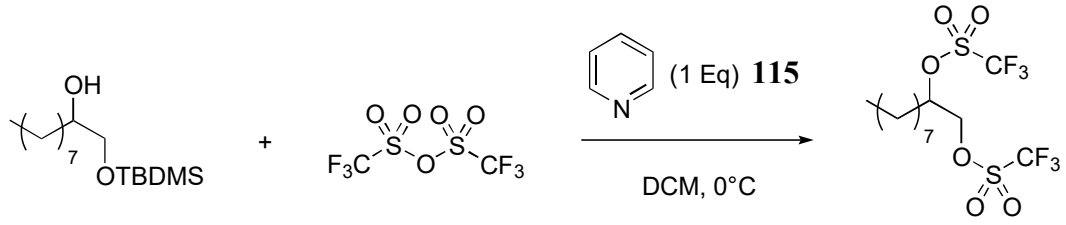


62 (1 Eq) + **114** (3 Eq) → **97**

Scheme 6.5: Synthesis of decane-1,2-diyl bis-(*p*-toluenesulfonate) **97**

The procedure was modified from literature [39]. To a stirred solution of decane-1,2-diol **62** (100 mg, 0.57 mmol) in anhydrous dichloromethane (5 mL) at room temperature under argon, dry triethylamine (0.32 mL, 2.3 mmol), 4-dimethylaminopyridine (70 mg, 0.57 mmol) and *p*-toluenesulfonyl chloride **114** (329 mg, 1.7 mmol) were added. The reaction was stirred at room temperature for 7 h, after which the mixture was diluted with diethyl ether (13 mL), followed by an addition of water (20 mL). The organic layer was washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography with *n*-hexane/EtOAc (83:17) to yield **97** (248 mg, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.69 (m, 4H), 7.35-7.30 (m, 4H), 4.61-4.53 (m, 1H), 4.03 (d, J = 4.7 Hz, 2H), 2.45 (s, 3H), 2.44 (s, 3H), 1.60-1.56 (m, 2H), 1.28-1.12 (m, 12H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 145.1, 133.6, 132.4, 130.0, 129.9, 128.1, 128.0, 79.0, 69.5, 31.9, 31.1, 29.3, 29.2, 29.1, 24.5, 22.7, 21.8, 14.2; HRMS (ESI) *m/z* calculated for $[C_{24}H_{34}O_6S_2 + Na]^+$ 505.1689, found 505.1712.

6.2.6 Decane-1,2-diyl bis(trifluoromethanesulfonate) (101)

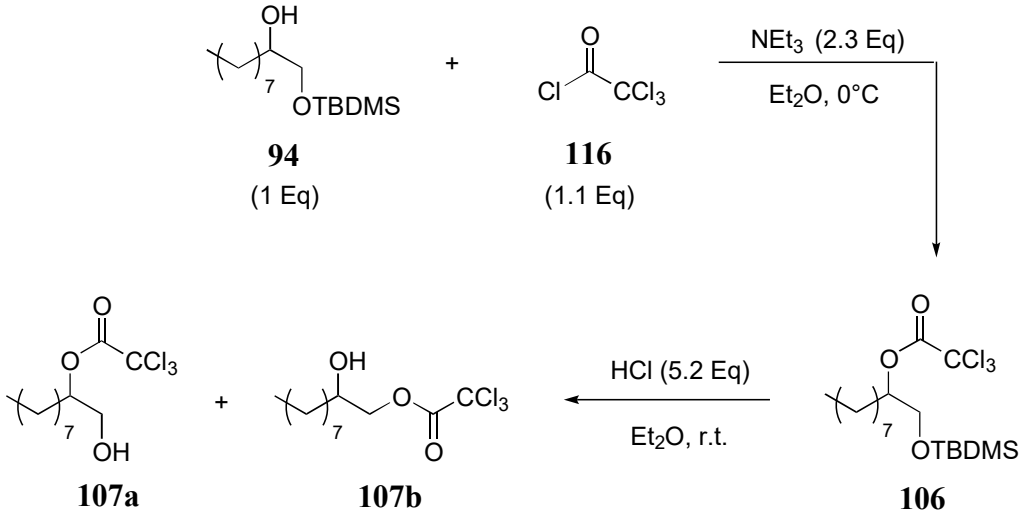


94 (1 Eq) + **100** (1 Eq) → **101**

Scheme 6.6: Synthesis of decane-1,2-diyl bis-(trifluoromethanesulfonate) **101**

The procedure was modified from literature [40]. Trifluoromethanesulfonic anhydride **100** (0.12 mL, 0.69 mmol) was dissolved into anhydrous dichloromethane (0.7 mL) at room temperature under argon. While stirring, the solution was cooled to 0 °C, after which a mixture of **95** (200 mg, 0.69 mmol) and pyridine **115** (56 μl, 0.69 mL) in dry dichloromethane (0.3 mL) was added dropwise over 10 min under argon. The mixture was stirred at room temperature for 18 h, after which the reaction mixture was washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with *n*-hexane/EtOAc (92.5:7.5) to yield **101** (119 mg, 39%) as a dark brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (dq, J = 2.6, 6.3 Hz, 1H), 4.69-4.55 (m, 2H), 2.00-1.78 (m, 2H), 1.49-1.28 (m, 12H), 0.91-0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.8, 120.6, 116.6, 116.4, 85.5, 74.3, 32.0, 31.9, 31.2, 29.7, 29.4, 29.2, 29.2, 29.1, 24.5, 22.8, 22.7, 14.2, 14.2; ^{19}F NMR (75 MHz, $CDCl_3$): δ -74.30 (s, 3H), -74.85 (s, 3H).

6.2.7 1-hydroxydec-2-yl 2,2,2-trichloroacetate (107a) and 2-hydroxydecyl 2,2,2-trichloroacetate (107b)



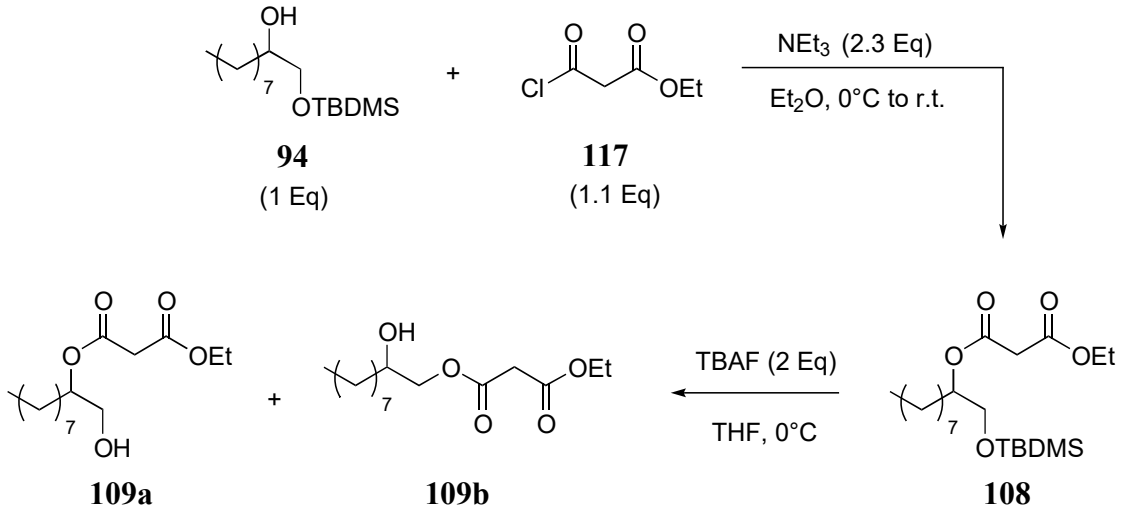
Scheme 6.7: Synthesis of 1-hydroxydec-2-yl 2,2,2-trichloroacetate **107a** and 2-hydroxydecyl 2,2,2-trichloroacetate **107b**

To a stirred solution of **94** (117 mg, 0.41 mmol) in anhydrous diethyl ether (1.5 mL) at 0 °C under argon, dry triethylamine (0.13 mL, 0.94 mmol) was added, followed by a drop-wise addition of trichloroacetyl chloride **116** (0.05 mL, 0.45 mmol). The reaction was stirred at 0 °C for 25 min, after which the formed precipitate was dissolved into a small amount of

water. The organic layer was washed with brine and dried over magnesium sulfate. The filtered product was concentrated under reduced pressure and **106** was obtained as a yellow oil (159 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08-5.00 (m, 1H), 3.73 (d, J = 5.3 Hz, 2H), 1.72-1.65 (m, 2H), 1.41-1.26 (m, 12H), 0.89-0.85 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 81.0, 64.0, 31.9, 30.2, 29.5, 29.4, 29.3, 25.9, 25.0, 22.8, 18.3, 14.3; HRMS (ESI) *m/z* calculated for $[C_{18}H_{35}Cl_3O_3Si + Na]^+$ 455.1313, found 455.1320.

To a stirred solution of **106** (299 mg, 0.69 mmol) in anhydrous diethyl ether (6 mL) at room temperature under argon, hydrochloric acid solution (1.8 mL, 2 M diethyl ether) was added dropwise. The reaction was stirred at room temperature for 66 h, after which saturated sodium bicarbonate solution (6.5 mL) was added. The aqueous layer was extracted three times with diethyl ether (1:1 ratio), after which the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with *n*-hexane/EtOAc (85:15) afforded the mixture of regioisomers **107a** and **107b** in a 1:1 ratio (138 mg, 63%). The mixture was a yellow oil in appearance. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11-5.03 (m, 1H, **107a**), 4.40-4.23 (m, 2H), 4.01-3.93 (m, 1H, **107b**), 3.86-3.72 (m, 2H), 1.81 (s, 2H), 1.77-1.64 (m, 2H), 1.58-1.49 (m, 2H), 1.44-1.26 (m, 22H), 0.89-0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 162.1, 81.4, 72.9, 69.5, 64.1, 33.2, 32.0, 31.9, 30.1, 29.6, 29.4, 29.4, 29.3, 29.3, 25.4, 25.1, 22.8, 14.2.

6.2.8 Ethyl (1-hydroxydec-2-yl) malonate (109a) and ethyl (2-hydroxydecyl) malonate (109b)

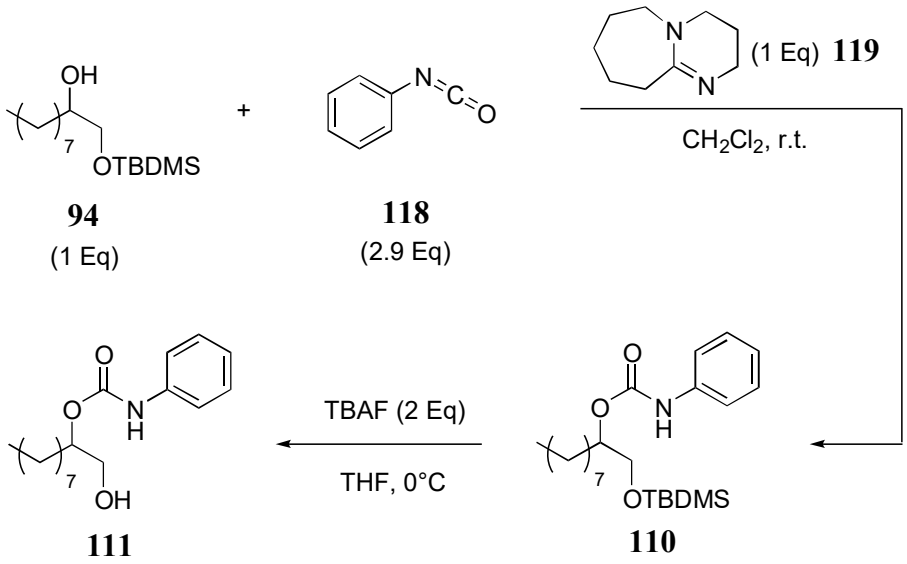


Scheme 6.8: Synthesis of ethyl (1-hydroxydec-2-yl) malonate **109a** and ethyl (2-hydroxydecyl) malonate **109b**

To a stirred solution of **94** (300 mg, 1 mmol) in anhydrous diethyl ether (4.5 mL) at 0 °C under argon, dry triethylamine (0.32 mL, 2.3 mmol) was added, followed by a dropwise addition of ethyl malonyl chloride **117** (0.14 mL, 1.1 mmol). The mixture was stirred at 0 °C for 30 min, warmed up to room temperature and stirred for 80 min, after which dry triethylamine (0.16 mL, 1.1 mmol) and ethyl malonyl chloride **117** (0.14 mL, 1.1 mmol) were added to push the reaction to completion. The reaction was stirred at room temperature for another 30 min, after which the precipitate was dissolved into a small amount of water. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography with *n*-hexane/tetrahydrofuran (95:5) to obtain **108** (267 mg, 64%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97-4.89 (m, 1H), 4.19 (q, J = 7.0 Hz, 2H), 3.63 (dd, J = 1.5, 5.0 Hz, 2H), 3.35 (s, 2H), 1.65-1.53 (m, 2H), 1.31-1.24 (m, 15H), 0.89-0.84 (m, 12H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 166.4, 110.2, 76.1, 64.2, 61.6, 42.0, 32.0, 30.5, 29.6, 29.6, 29.4, 25.9, 25.2, 22.8, 18.4, 14.3, 14.2.

To a stirred solution of **108** (259 mg, 0.64 mmol) in anhydrous tetrahydrofuran (2.5 mL) at 0 °C under argon, dry tetra-*n*-butylammonium fluoride solution (1.3 mL, 1 M tetrahydrofuran) was added dropwise. The reaction was stirred at room temperature for 2 h, after which the mixture was quenched with saturated ammonium chloride solution (1.5 mL) and a few drops of water. The aqueous layer was extracted three times with dichloromethane (1:1 ratio), after which the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography with *n*-hexane/ethyl acetate (72:28) to obtain the mixture of regioisomers **109a** and **109b** (131 mg, 71%) in a 5:8 ratio. The mixture was a colorless oil in appearance. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (dd, J = 6.4, 2.9 Hz, 0.61H, **109a**), 4.24-4.16 (m, 4H), 4.05-3.99 (m, 1H, **109b**), 3.90-3.81 (m, 1H, **109b**), 3.76-3.69 (m, 0.65H, **109a**), 3.63-3.55 (m, 0.68H, **109a**), 3.41 (s, 2H, **109b**), 3.39 (s, 1.2H, **109a**), 2.52-2.48 (m, 1H, **109a**), 2.40 (d, J = 4.1 Hz, 1H, **109b**), 1.62-1.53 (m, 1H), 1.51-1.43 (m, 3H), 1.30-1.25 (m, 22H), 0.93-0.79 (t, J = 7.0 Hz, 4.3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 167.0, 166.7, 166.7, 77.1, 69.7, 69.6, 64.4, 62.0, 61.9, 41.9, 41.6, 33.2, 32.0, 31.9, 30.4, 29.7, 29.6, 29.5, 29.3, 29.3, 25.5, 25.3, 22.8, 14.2, 14.2.

6.2.9 1-hydroxydec-2-yl phenylcarbamate (111)



Scheme 6.9: Synthesis of 1-hydroxydec-2-yl phenylcarbamate **111**

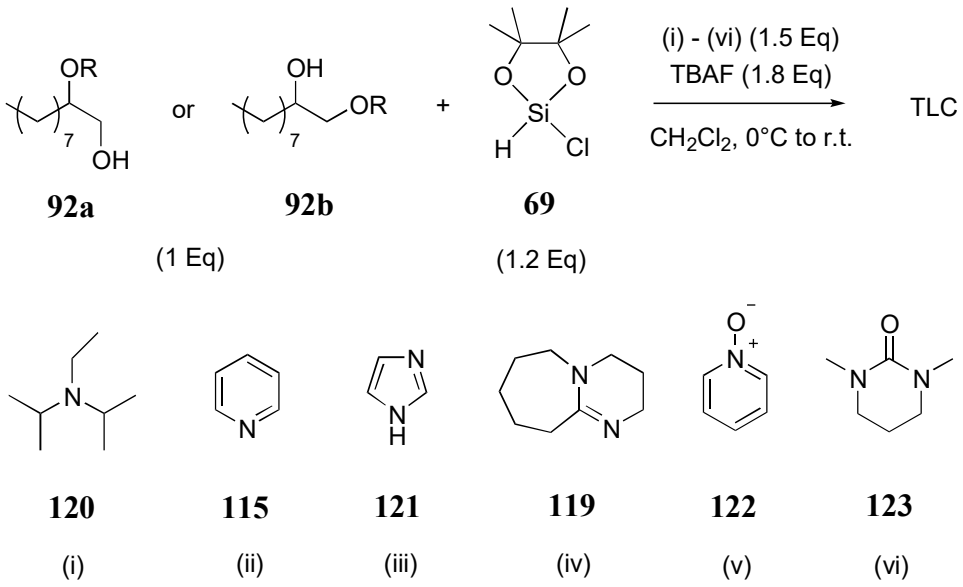
To a stirred solution of **94** (902 mg, 3.13 mmol) in anhydrous dichloromethane (9 mL) at room temperature under argon, 1,8-diazabicyclo[5.4.0]undec-7-ene **119** (0.47 mL, 3.14 mmol) and phenyl isocyanate **118** (1 mL, 9.2 mmol) were added. The reaction was stirred at room temperature for 14 h, after which the reaction mixture was treated with saturated ammonium chloride solution. The organic layer was washed with saturated brine and water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with toluene to yield **110** (1 g, 79%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 8.2 Hz, 2H), 7.33-7.28 (m, 2H), 7.08-7.03 (m, 1H), 6.60 (s, 1H), 4.91-4.83 (m, 1H), 3.70 (d, J = 5.3 Hz, 2H), 1.67-1.58 (m, 2H), 1.41-1.27 (m, 12H), 0.90-0.88 (m, 12H), 0.07 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 138.2, 129.2, 123.4, 118.8, 75.8, 64.6, 32.0, 30.8, 29.7, 29.6, 29.4, 26.0, 25.4, 22.8, 18.4, 14.3.

To a stirred solution of **110** (973 mg, 2.4 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C under argon, dry tetra-*n*-butylammonium fluoride solution (4.8 mL, 1 M tetrahydrofuran) was added dropwise. The reaction was stirred at 0 °C for 90 min, after which the mixture was quenched with saturated ammonium chloride solution (12 mL) and a few drops of water. The aqueous layer was extracted three times with dichloromethane, after which the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Silica gel column chromatography with *n*-hexane/ethyl acetate (7:3)

afforded **111** (610 mg, 87%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, J = 8.4 Hz, 2H), 7.32-7.26 (m, 2H), 7.08-7.03 (m, 1H), 6.93 (s, 1H), 4.92-4.85 (m, 1H), 3.80-3.63 (m, 2H), 2.57 (s, 1H), 1.66-1.54 (m, 2H), 1.39-1.26 (m, 12H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 137.9, 129.2, 123.7, 118.9, 76.9, 65.1, 32.0, 30.9, 29.6, 29.6, 29.4, 25.5, 22.8, 14.2.

6.3 TLC-monitored PCS-reactions with different Lewis bases

6.3.1 General procedure



Scheme 6.10: General Procedure for the TLC-experiments with PCS

To a stirred solution of a decane-1,2-diol derivative **92a** or **92b** (20 mg) in anhydrous dichloromethane (0.3 mL) at room temperature under argon, dry *N*,*N*-diisopropylethyl-amine **120** was added. The same process was repeated for five identical solutions with dry Lewis bases **115**, **121**, **119**, **122** and **123**. A stock solution of PCS **69** was distributed dropwise to the reaction mixtures (0.11 mL each) at 0 °C under argon, so that the amount of PCS in each reaction was 1.2 Equivalents. The mixtures were stirred at 0 °C for 20 minutes, warmed up to room temperature and stirred for over 20 hours. Dry tetra-*n*-butylammonium fluoride solution was added dropwise at room temperature, after which the resulting mixtures were each stirred for 1 h at room temperature. The reactions were each quenched with saturated ammonium chloride solution (0.1 mL). The progress of

the reactions was monitored simultaneously via TLC at the following intervals: first analysis within 1 h from the start of the reaction, second analysis right before the addition of tetra-*n*-butylammonium fluoride solution, third analysis 1 h after the addition of tetra-*n*-butylammonium fluoride solution and the final analysis after the reactions were quenched. After the formation of new products was detected, the corresponding reactions were scaled up as described in section 6.4.

6.3.2 TLC-monitored PCS-reactions of (98)

Following the general procedure, 2-(*p*-toluenesulfonyl)decan-1-ol **98** (20 mg, 0.06 mmol) was dissolved in anhydrous dichloromethane (0.3 mL) and treated with dry *N*,*N*-diisopropylethylamine **120** (16 μl, 0.09 mmol), a solution of PCS **69** (0.11 mL, 0.67 M in dry dichloromethane) and dry tetra-*n*-butylammonium fluoride solution (0.11 mL, 1 M in tetrahydrofuran). The procedure was repeated for five other reactions with dry pyridine **115** (7.4 μl, 0.09 mmol), imidazole solution **121** (0.05 mL, 2 M in dry dichloromethane), 1,8-diazabicyclo[5.4.0]undec-7-ene **119** (14 μl, 0.09 mmol), pyridine-*N*-oxide solution **122** (0.05 mL, 1.9 M in dry dichloromethane) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone **123** (11 μl, 0.09 mmol).

6.3.3 TLC-monitored PCS-reactions of (107a) and (107b)

Following the general procedure, the mixture of 1-hydroxydec-2-yl 2,2,2-trichloroacetate **107a** and 2-hydroxydecyl 2,2,2-trichloroacetate **107b** (20 mg, 0.06 mmol) was dissolved in anhydrous dichloromethane (0.3 mL) and treated with dry *N*,*N*-diisopropylethylamine **120** (16.5 μl, 0.09 mmol), a solution of PCS **69** (0.11 mL, 0.69 M in dry dichloromethane) and dry tetra-*n*-butylammonium fluoride solution (0.11 mL, 1 M in tetrahydrofuran). The procedure was repeated for five other reactions with dry pyridine **115** (7.6 μl, 0.09 mmol), imidazole solution **121** (0.05 mL, 1.9 M in dry dichloromethane), 1,8-diazabicyclo[5.4.0]-undec-7-ene **119** (14 μl 0.09 mmol), pyridine-*N*-oxide solution **122** (0.05 mL, 1.9 M in dry dichloromethane) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone **123** (11.5 μl, 0.09 mmol).

6.3.4 TLC-monitored PCS-reactions of (109a) and (109b)

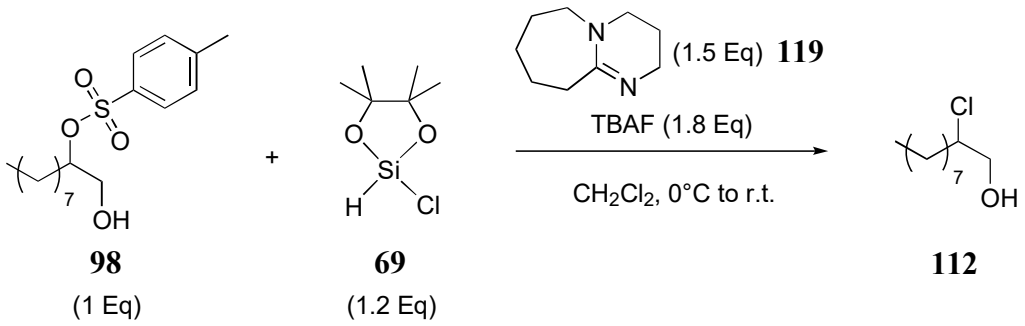
Following the general procedure, the mixture of ethyl (1-hydroxydec-2-yl) malonate **109a** and ethyl (2-hydroxydecyl) malonate **109b** (20 mg, 0.07 mmol) was dissolved in anhydrous dichloromethane (0.3 mL) and treated with dry *N*,*N*-diisopropylethylamine **120** (18 μl, 0.1 mmol), a solution of PCS **69** (0.11 mL, 0.75 M in dry dichloromethane) and dry tetra-*n*-butylammonium fluoride solution (0.13 mL, 1 M in tetrahydrofuran). The procedure was repeated for five other reactions with dry pyridine **115** (8.4 μl, 0.1 mmol), imidazole solution **121** (0.05 mL, 2.1 M in dry dichloromethane), 1,8-diazabicyclo[5.4.0]-undec-7-ene **119** (15.5 μl, 0.1 mmol), pyridine-*N*-oxide solution **122** (0.05 mL, 2.1 M in dry dichloromethane) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone **123** (12.5 μl, 0.1 mmol).

6.3.5 TLC-monitored PCS-reactions of (111)

Following the general procedure, 1-hydroxydec-2-yl phenylcarbamate **111** (20 mg, 0.07 mmol) was dissolved in anhydrous dichloromethane (0.3 mL) and treated with dry *N*,*N*-diisopropylethylamine **120** (18 μl, 0.1 mmol), a solution of PCS **69** (0.11 mL, 0.75 M in dry dichloromethane) and dry tetra-*n*-butylammonium fluoride solution (0.12 mL, 1 M in tetrahydrofuran). The procedure was repeated for five other reactions with dry pyridine **115** (8.2 μl, 0.1 mmol), imidazole solution **121** (0.05 mL, 2 M in dry dichloromethane), 1,8-diazabicyclo[5.4.0]undec-7-ene **119** (15.5 μl, 0.1 mmol), pyridine-*N*-oxide solution **122** (0.05 mL, 2 M in dry dichloromethane) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone **123** (12.5 μl, 0.1 mmol).

6.4 Reactions with PCS

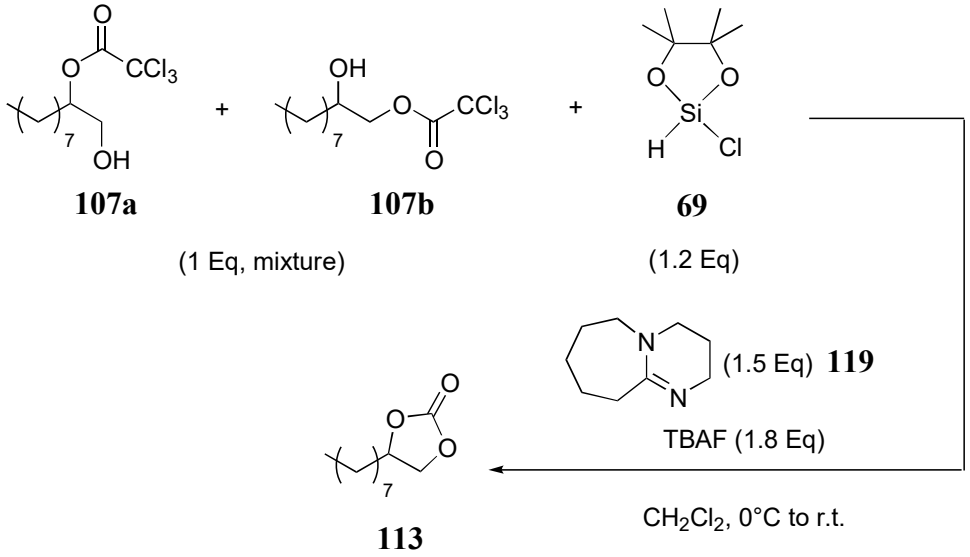
6.4.1 Synthesis of 2-chlorodecan-1-ol (112)



Scheme 6.11: Synthesis of 2-chlorodecan-1-ol **112**

To a stirred solution of **98** (50 mg, 0.15 mmol) in anhydrous dichloromethane (0.75 mL) at 0 °C under argon, 1,8-diazabicyclo[5.4.0]undec-7-ene **119** (34 μl, 0.23 mmol) was added. Under argon, PCS **69** (33 mg, 0.18 mmol) was dissolved into anhydrous dichloromethane (0.3 mL) and the solution was added dropwise to the reaction mixture at 0 °C. The resulting mixture was stirred at 0 °C for 20 min, warmed up to room temperature and stirred for 50 h. Dry tetra-*n*-butylammonium fluoride solution (0.27 mL, 1 M tetrahydrofuran) was added dropwise at room temperature and the mixture was stirred for 20 min. The reaction was quenched with saturated ammonium chloride solution (1 mL) and a few drops of water, after which the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography in two steps, first with *n*-hexane/EtOAc (95:5) and then with *n*-hexane/EtOAc (85:15), to obtain **112** (4 mg, 12%) as a colorless oil. **112** was obtained with similar spectral characterization as reported in literature [52]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07-3.99 (m, 1H), 3.82-3.63 (m, 2H), 1.83-1.65 (m, 2H), 1.58-1.25 (m, 12H), 0.88 (t, J = 6.4 Hz, 3H).

6.4.2 Synthesis of 4-octyl-1,3-dioxolan-2-one (113)



Scheme 6.12: Synthesis of 4-octyl-1,3-dioxolan-2-one **113**

To a stirred solution of the mixture of **107a** and **107b** (50 mg, 0.16 mmol) in anhydrous dichloromethane (0.75 mL) at 0 °C under argon, 1,8-diazabicyclo[5.4.0]undec-7-ene **119** (35 μl, 0.23 mmol) was added. Under argon, PCS **69** (35 mg, 0.19 mmol) was dissolved into anhydrous dichloromethane (0.3 mL) and the solution was added dropwise to the reaction mixture at 0 °C. The resulting mixture was stirred at 0 °C for 45 min, warmed up to room temperature and stirred for 3 h. Dry tetra-*n*-butylammonium fluoride solution (0.28 mL, 1 M tetrahydrofuran) was added dropwise at room temperature and the mixture was stirred for 30 min. The reaction was quenched with saturated ammonium chloride solution (0.5 mL) and a few drops of water, after which the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with *n*-hexane/ethyl acetate (8:2) to afford **113** (25 mg, 80%) as a colorless oil. **113** was obtained with similar spectral characterization as reported in literature [50]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74-4.65 (m, 1H), 4.52 (t, J = 8.2 Hz, 1H), 4.06 (dd, J = 7.0, 8.2 Hz, 1H), 1.86-1.76 (m, 1H), 1.72-1.61 (m, 1H), 1.51-1.43 (m, 1H), 1.40-1.26 (m, 12H), 0.87 (t, J= 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 77.1, 69.5, 34.0, 31.9, 29.4, 29.2, 29.2, 24.5, 22.7, 14.2.

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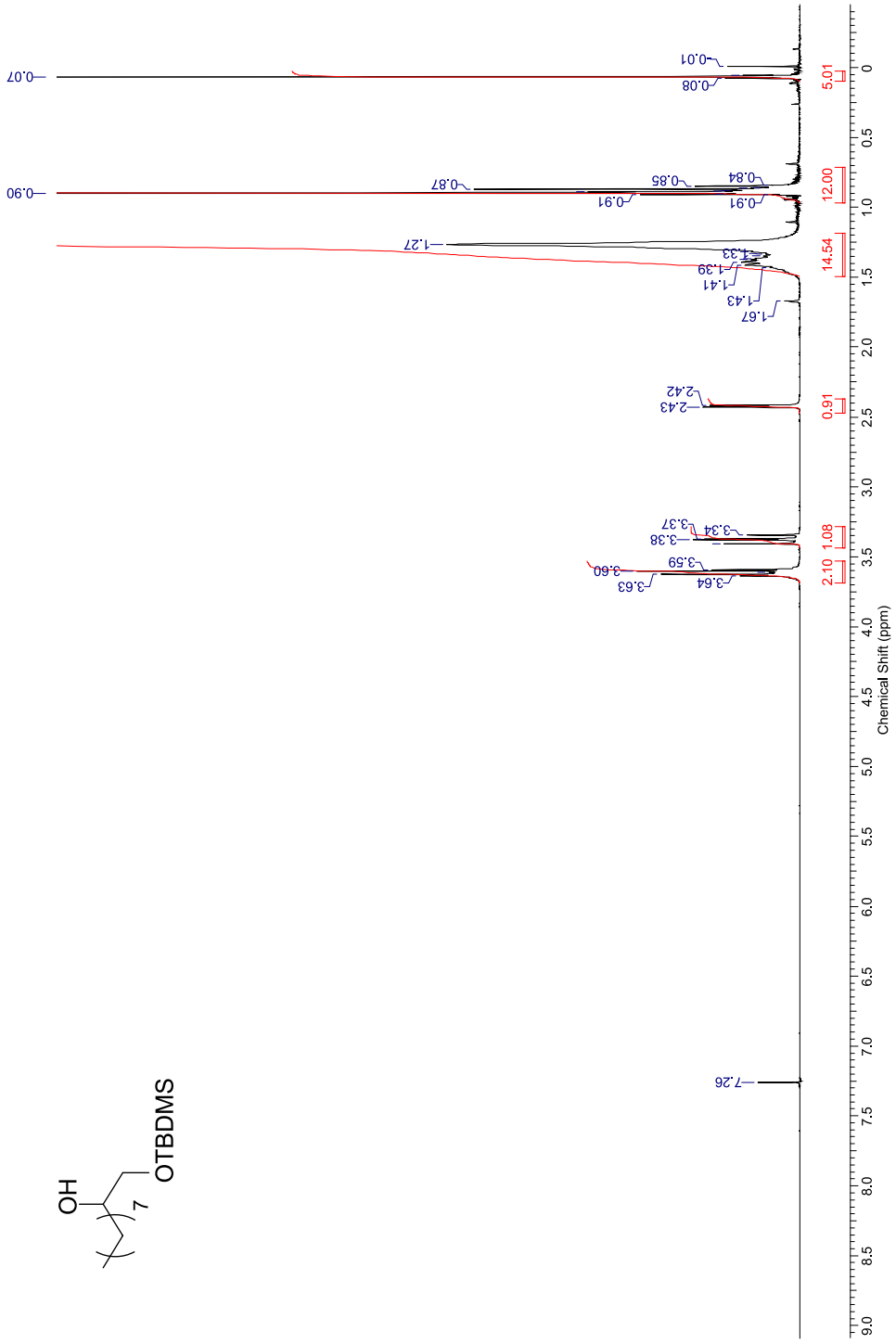
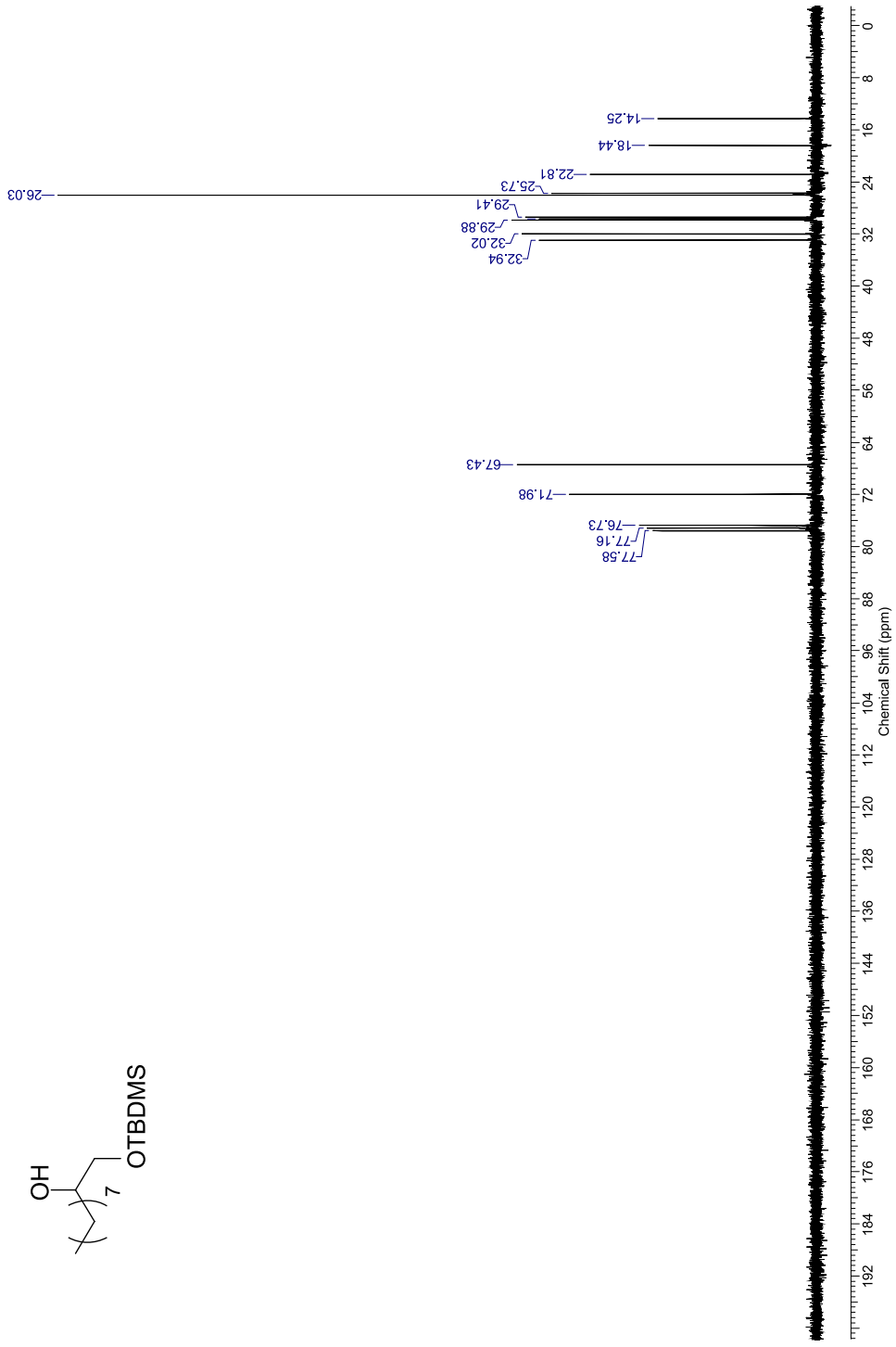
Appendices

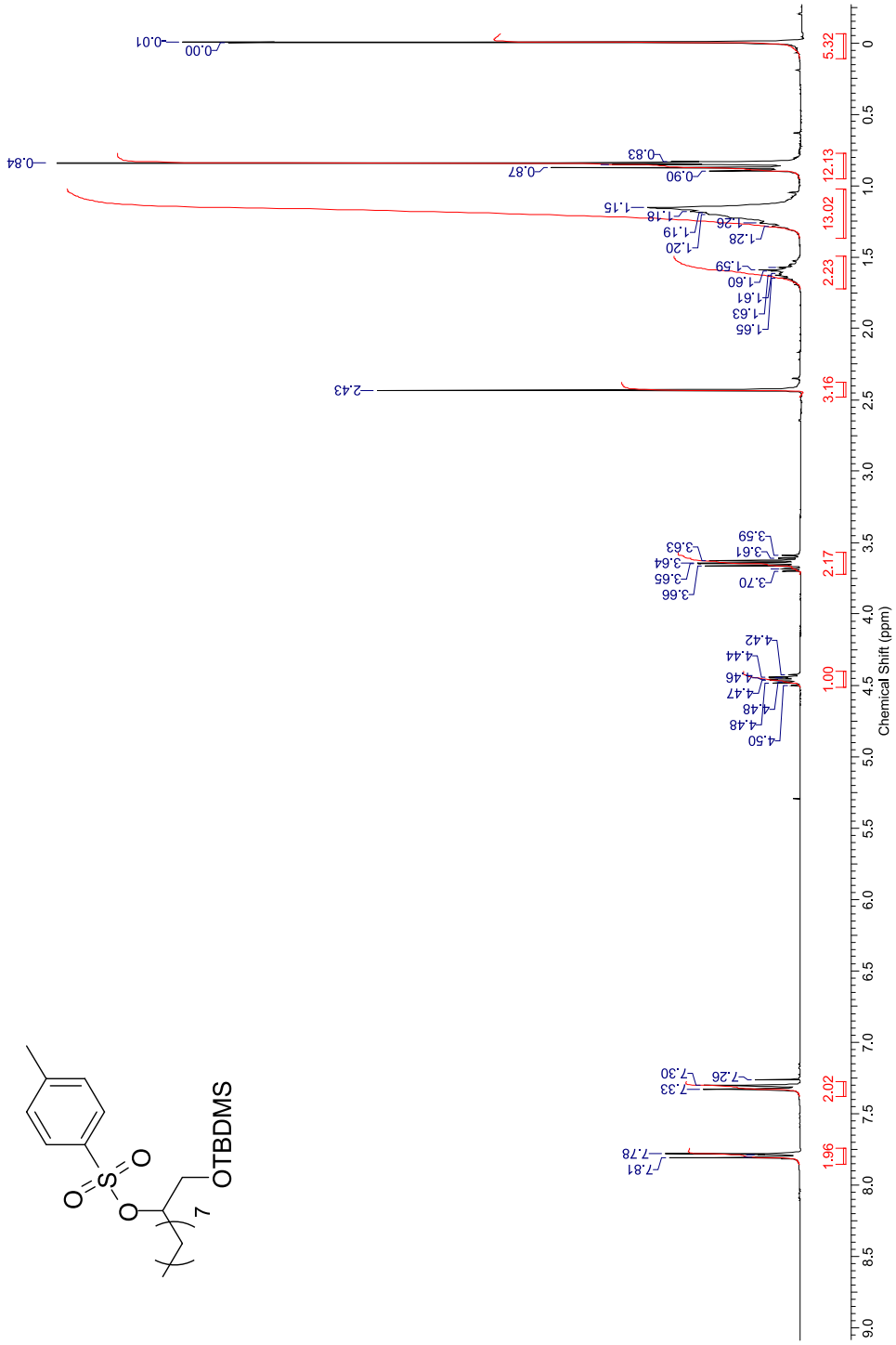
Appendix 1: ^{1}H NMR spectra of (94)



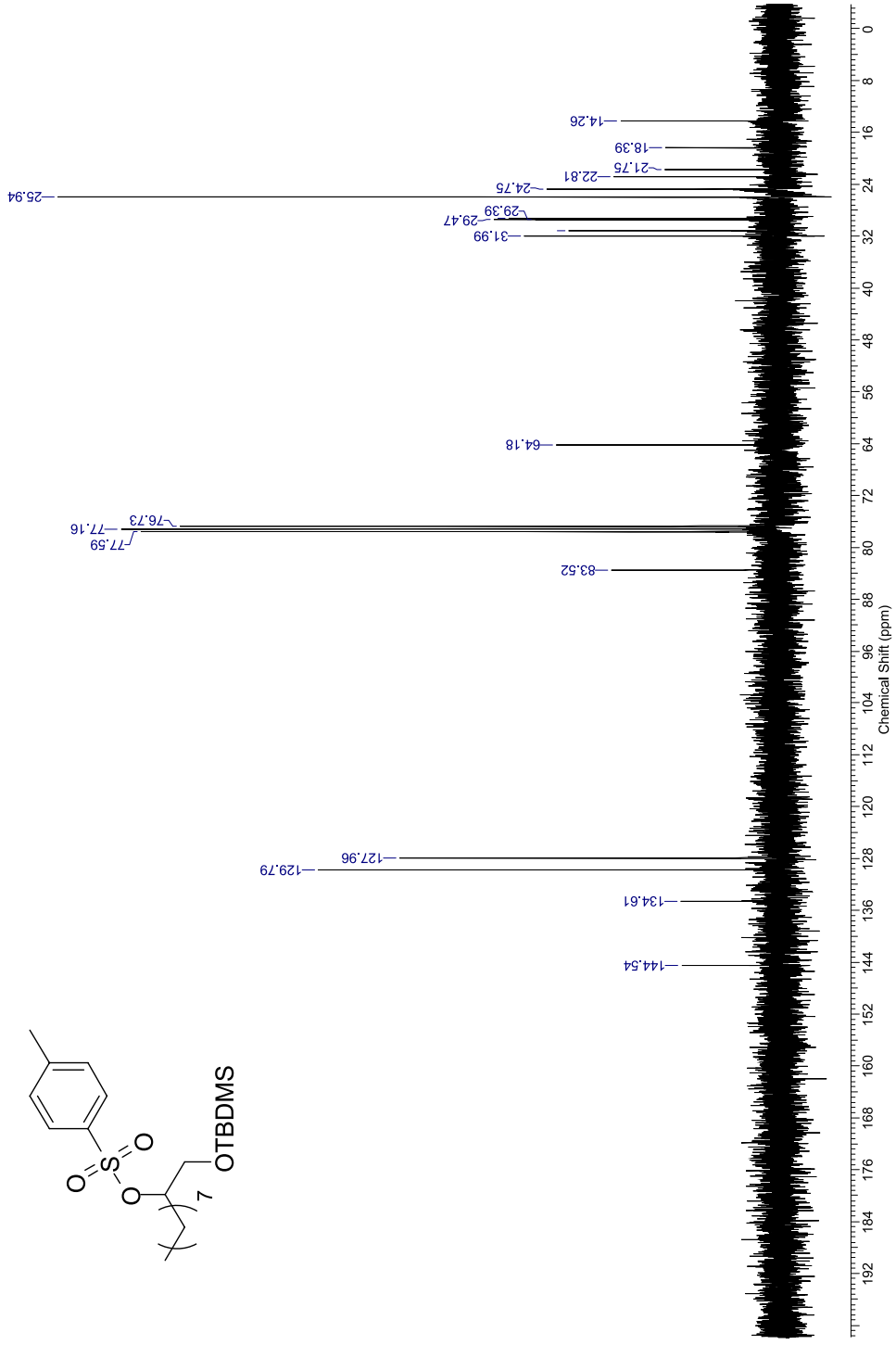
Appendix 2: ^{13}C NMR spectra of (94)



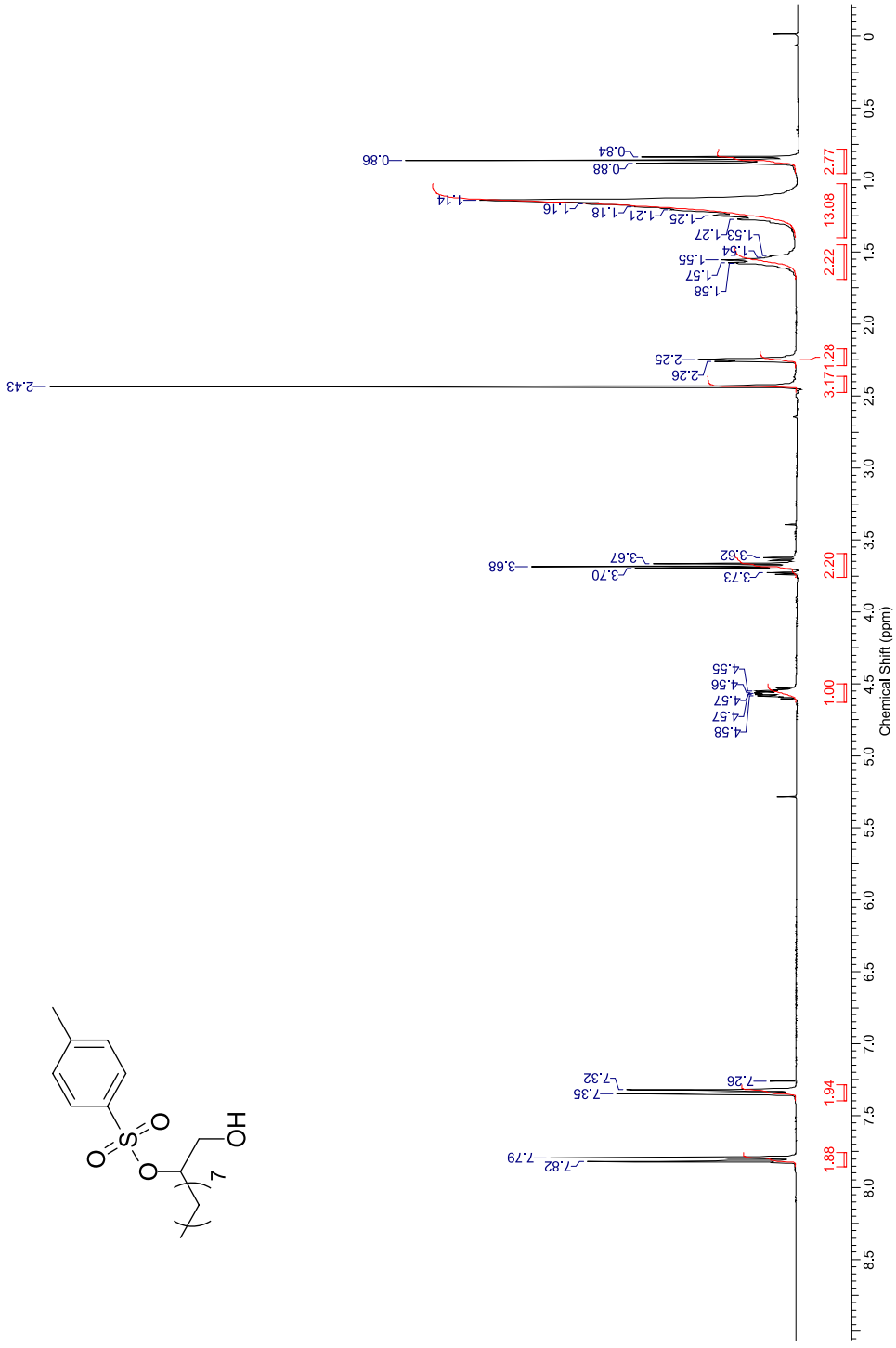
Appendix 3: ^{1}H NMR spectra of (95)



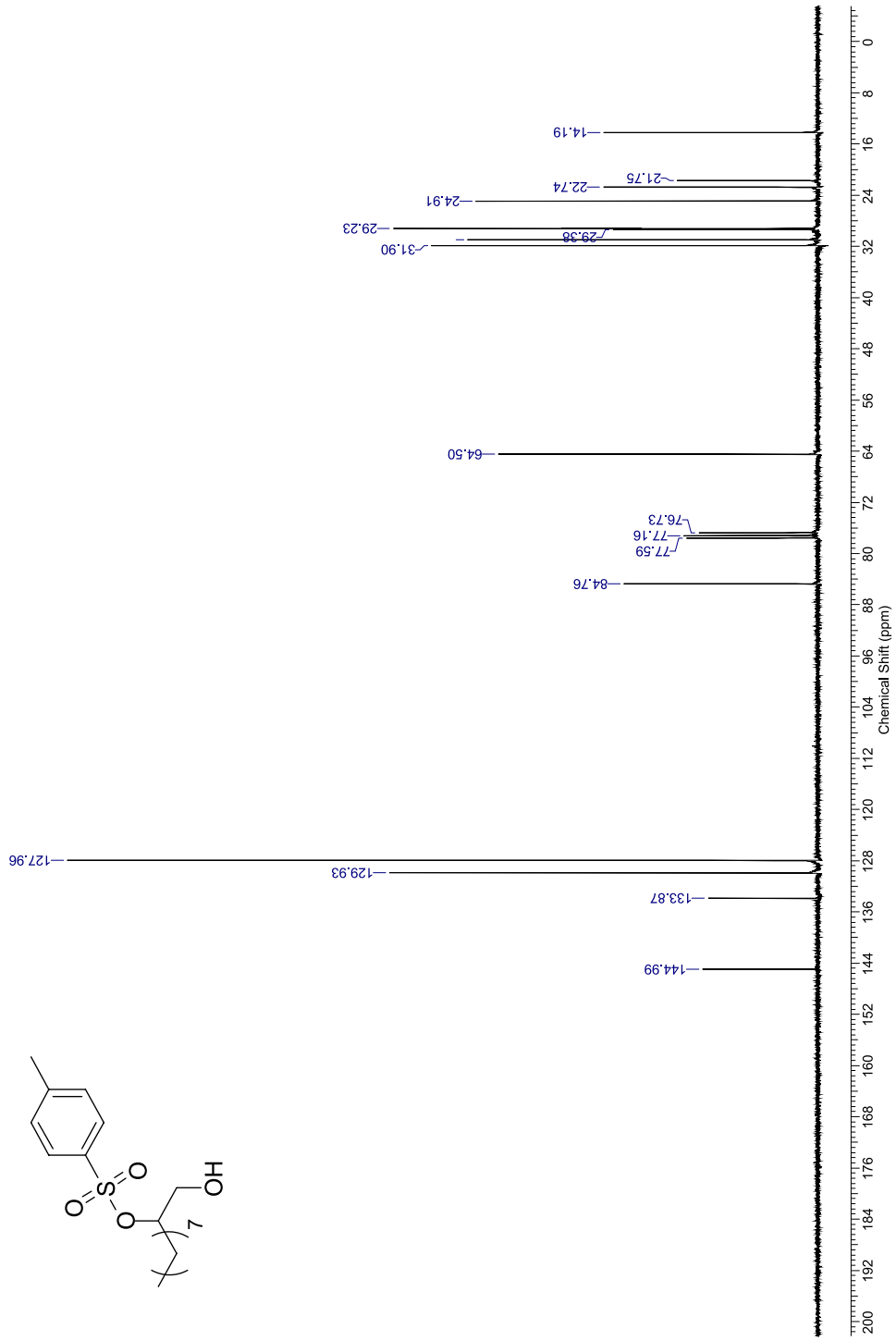
Appendix 4: ^{13}C NMR spectra of (95)



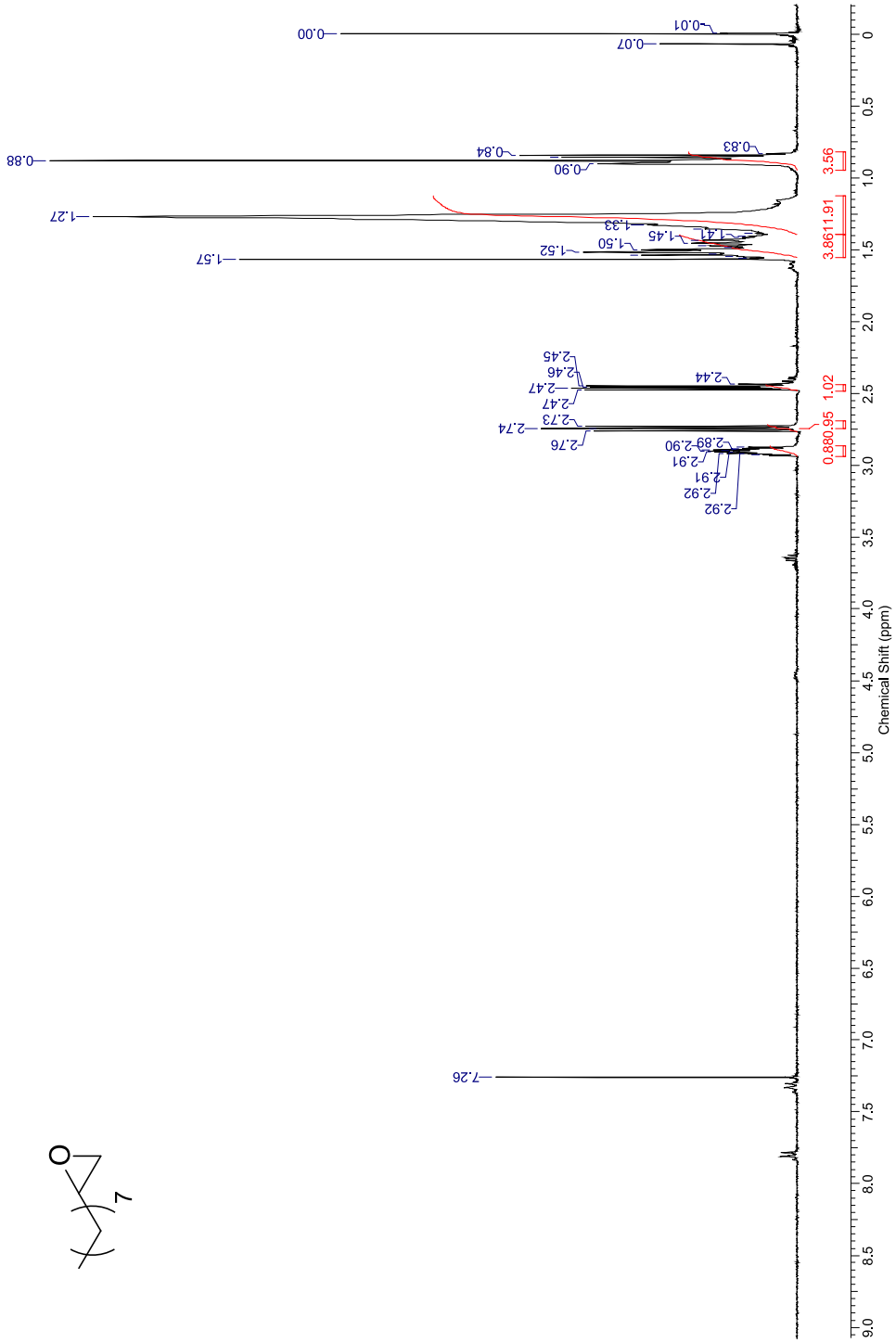
Appendix 5: ^{1}H NMR spectra of (98)



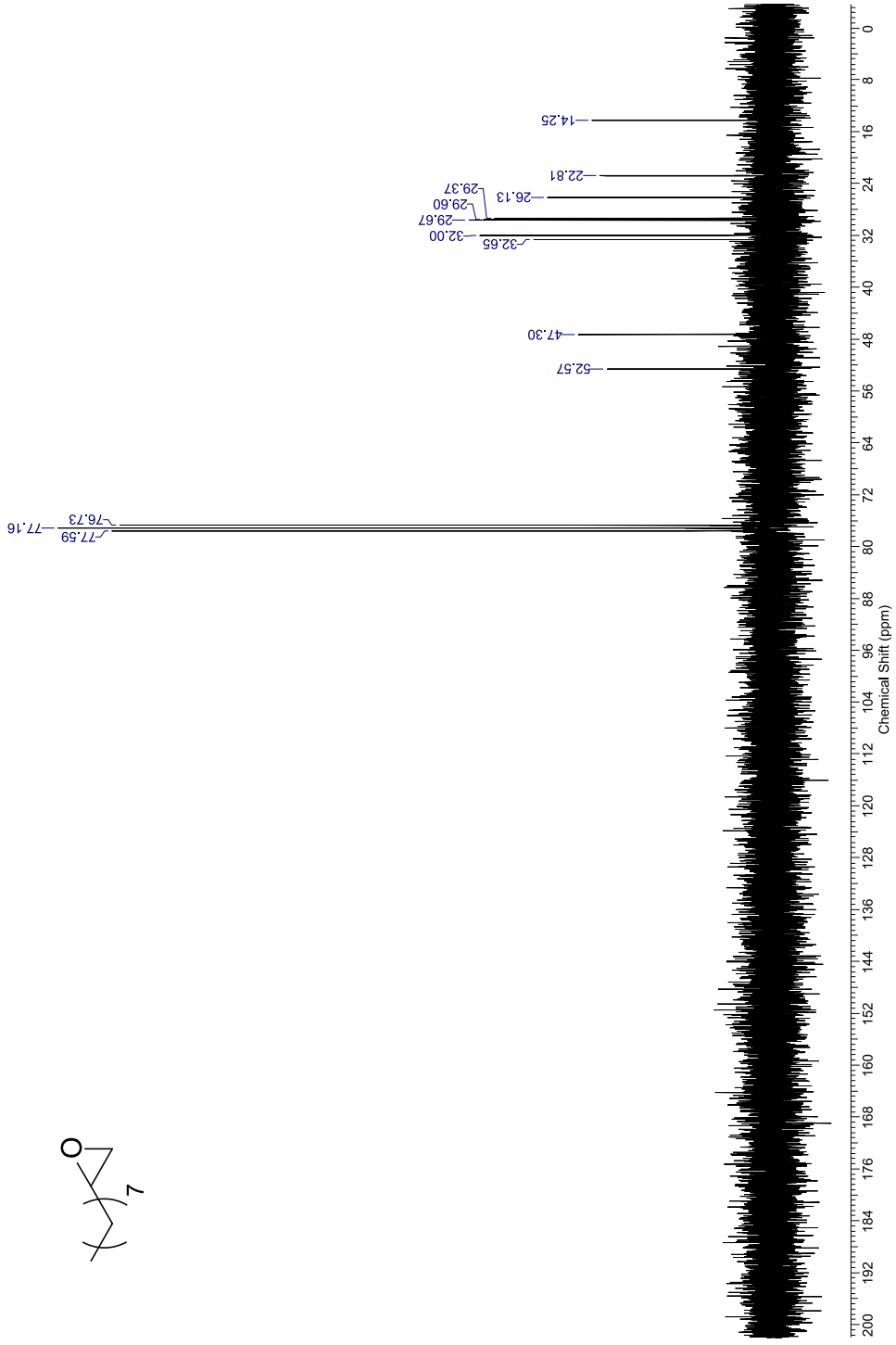
Appendix 6: ^{13}C NMR spectra of (98)



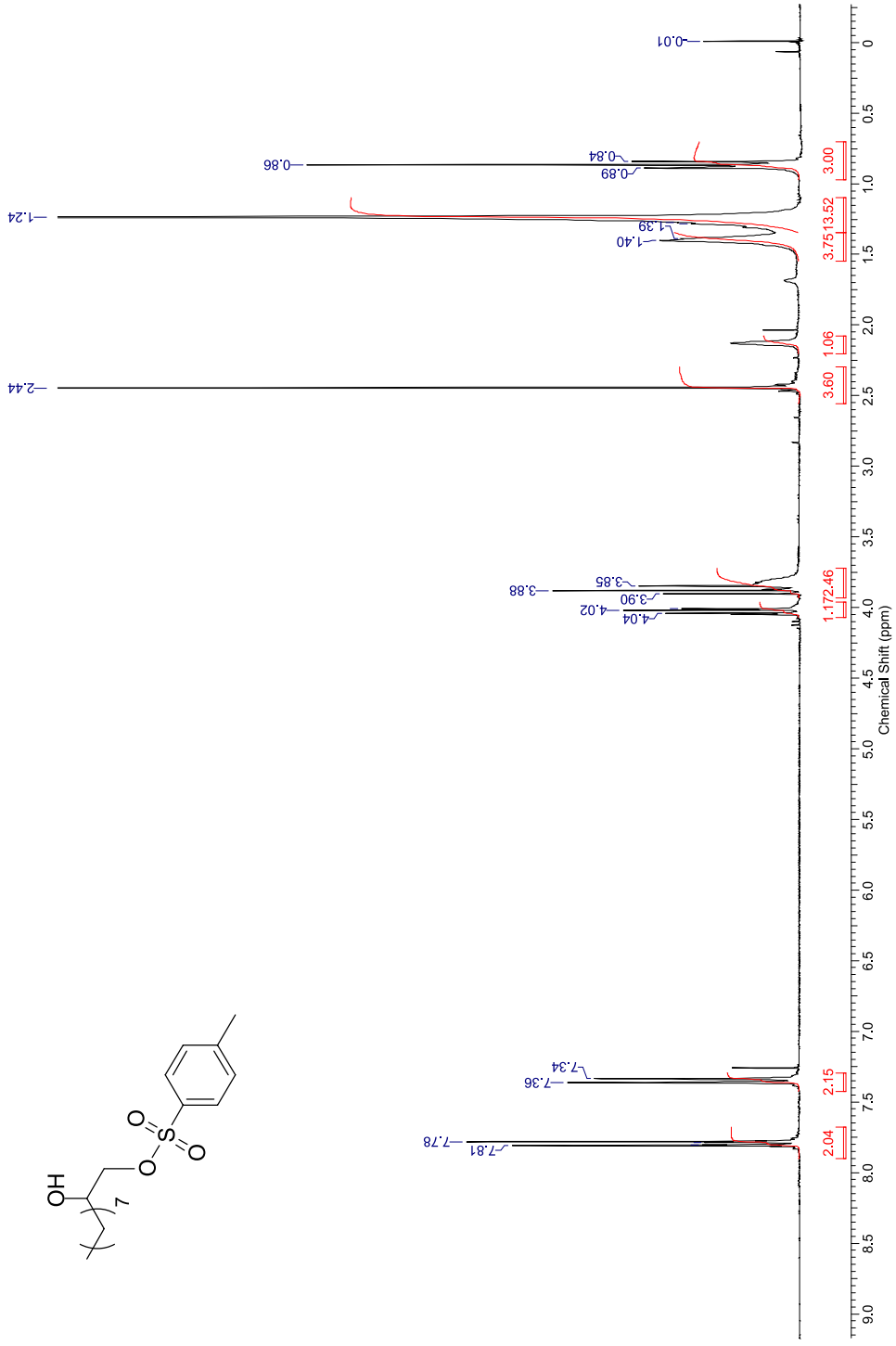
Appendix 7: ^{1}H NMR spectra of (99)



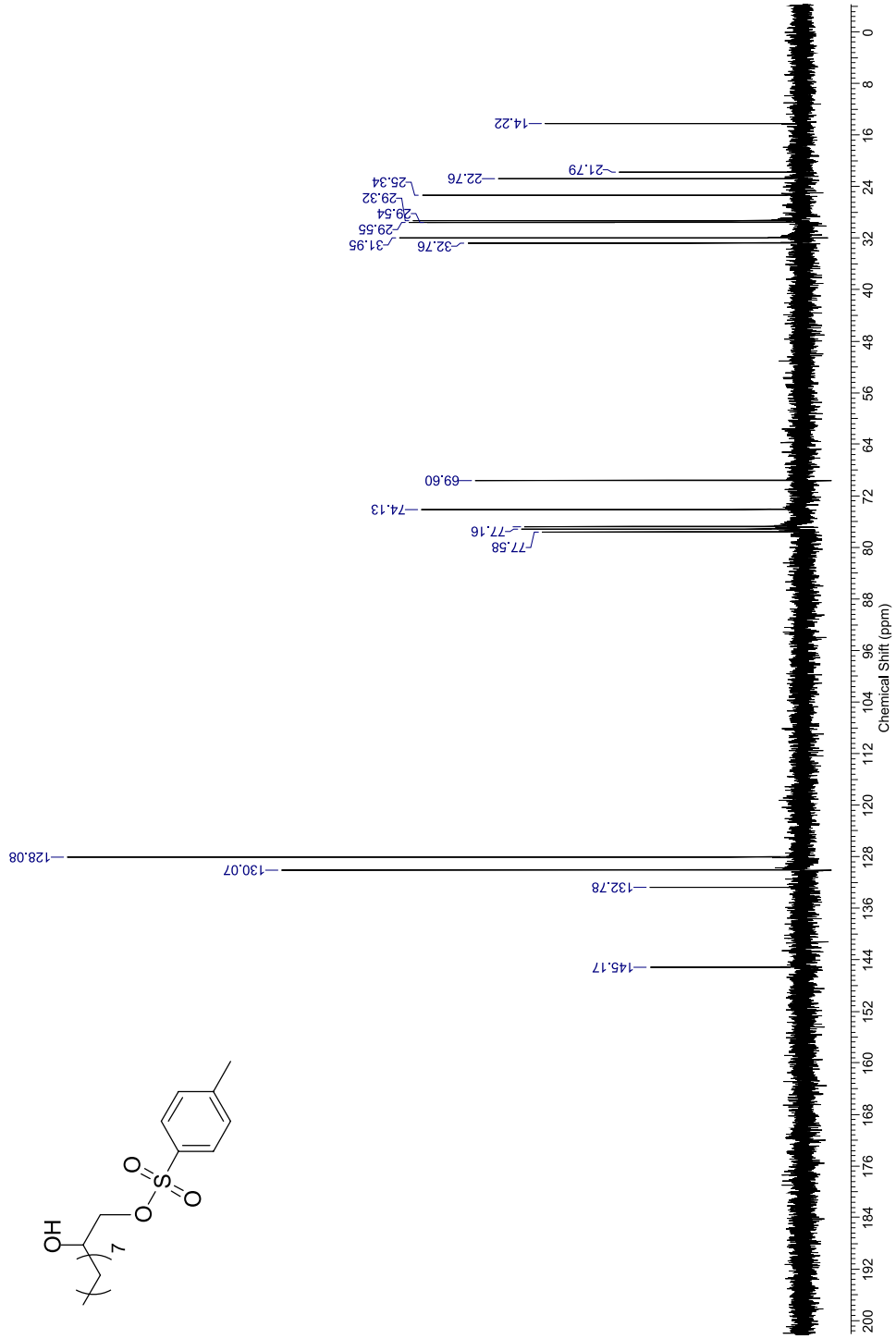
Appendix 8: ^{13}C NMR spectra of (99)



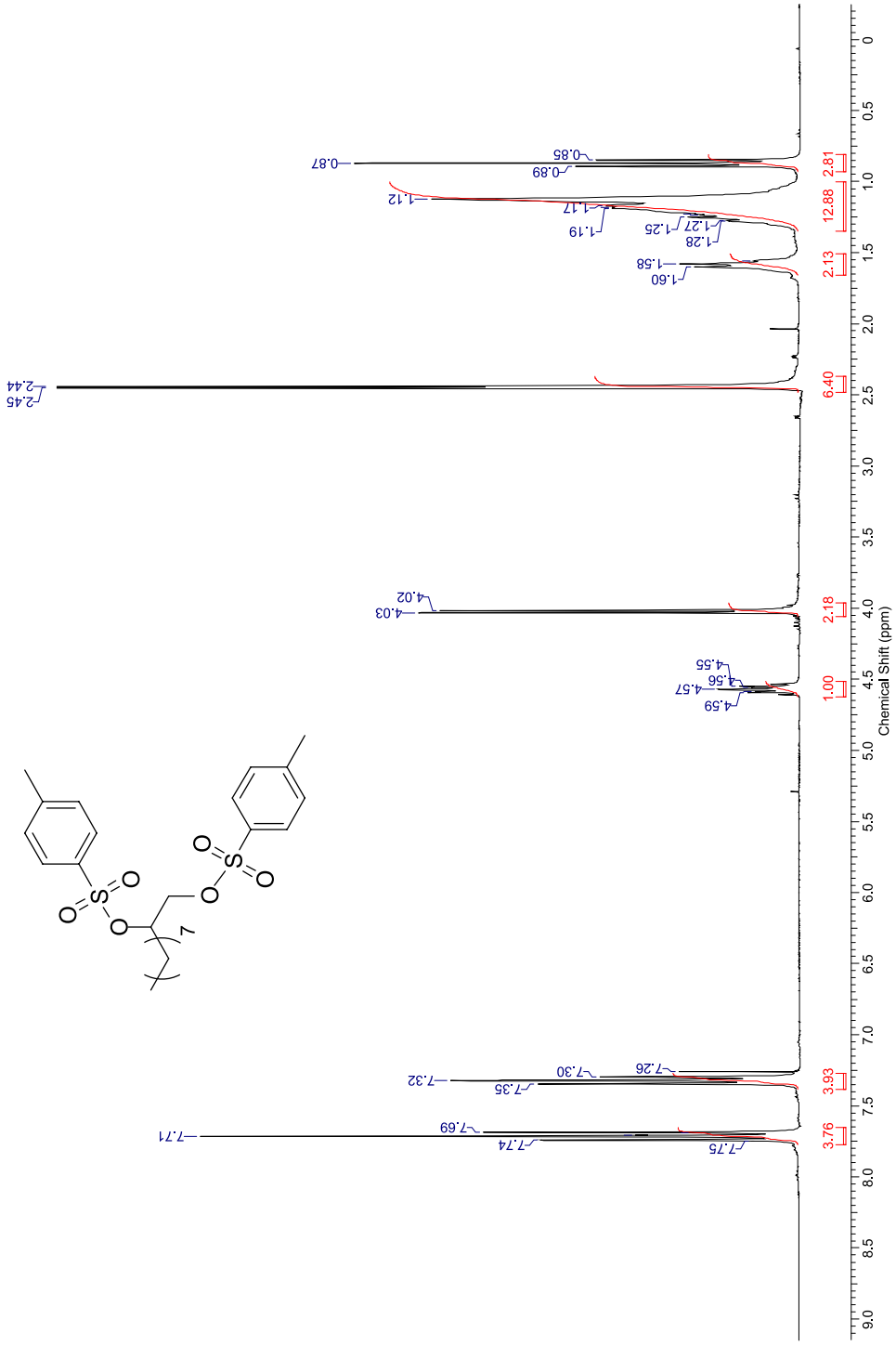
Appendix 9: ^{1}H NMR spectra of (96)



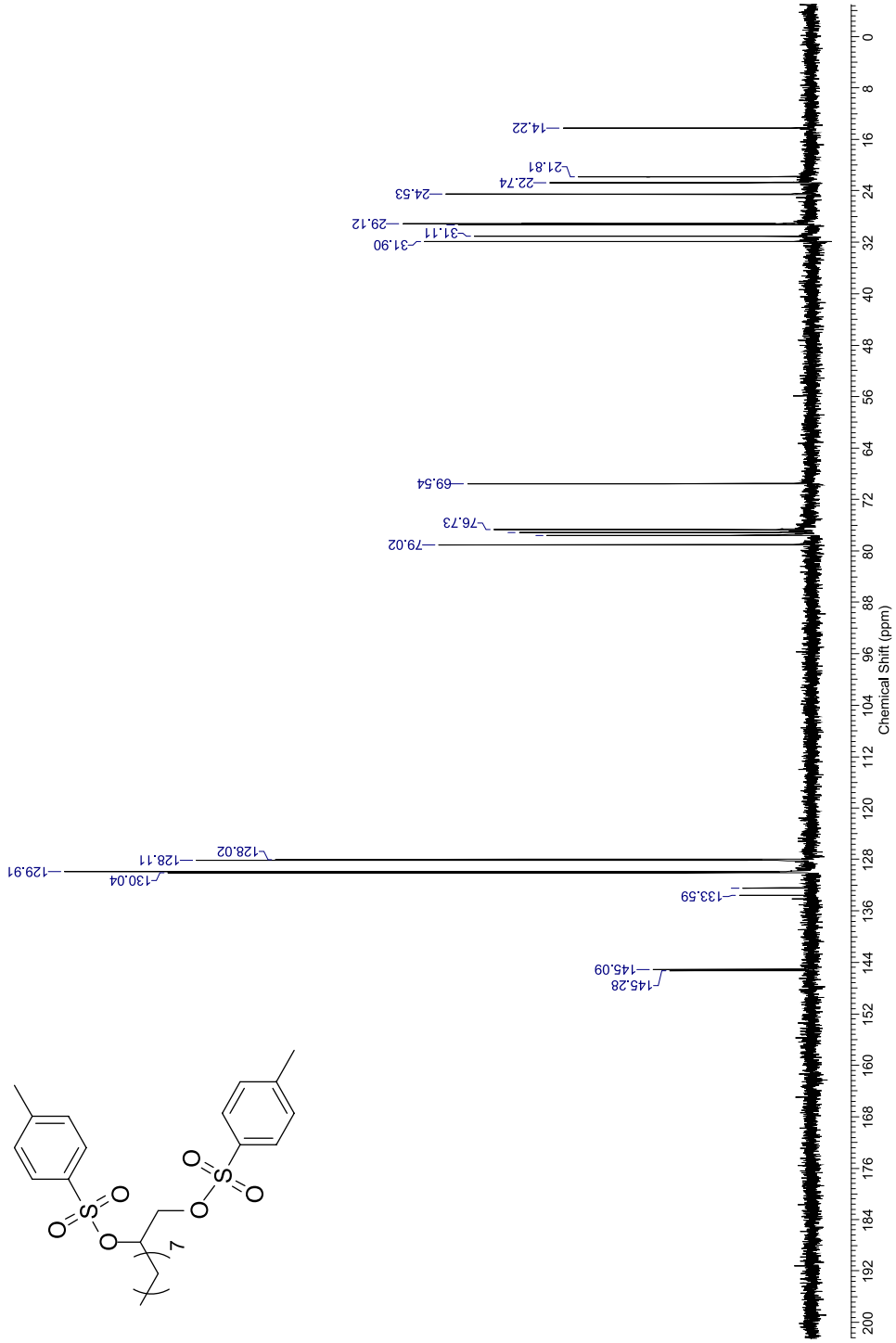
Appendix 10: ^{13}C NMR spectra of (96)



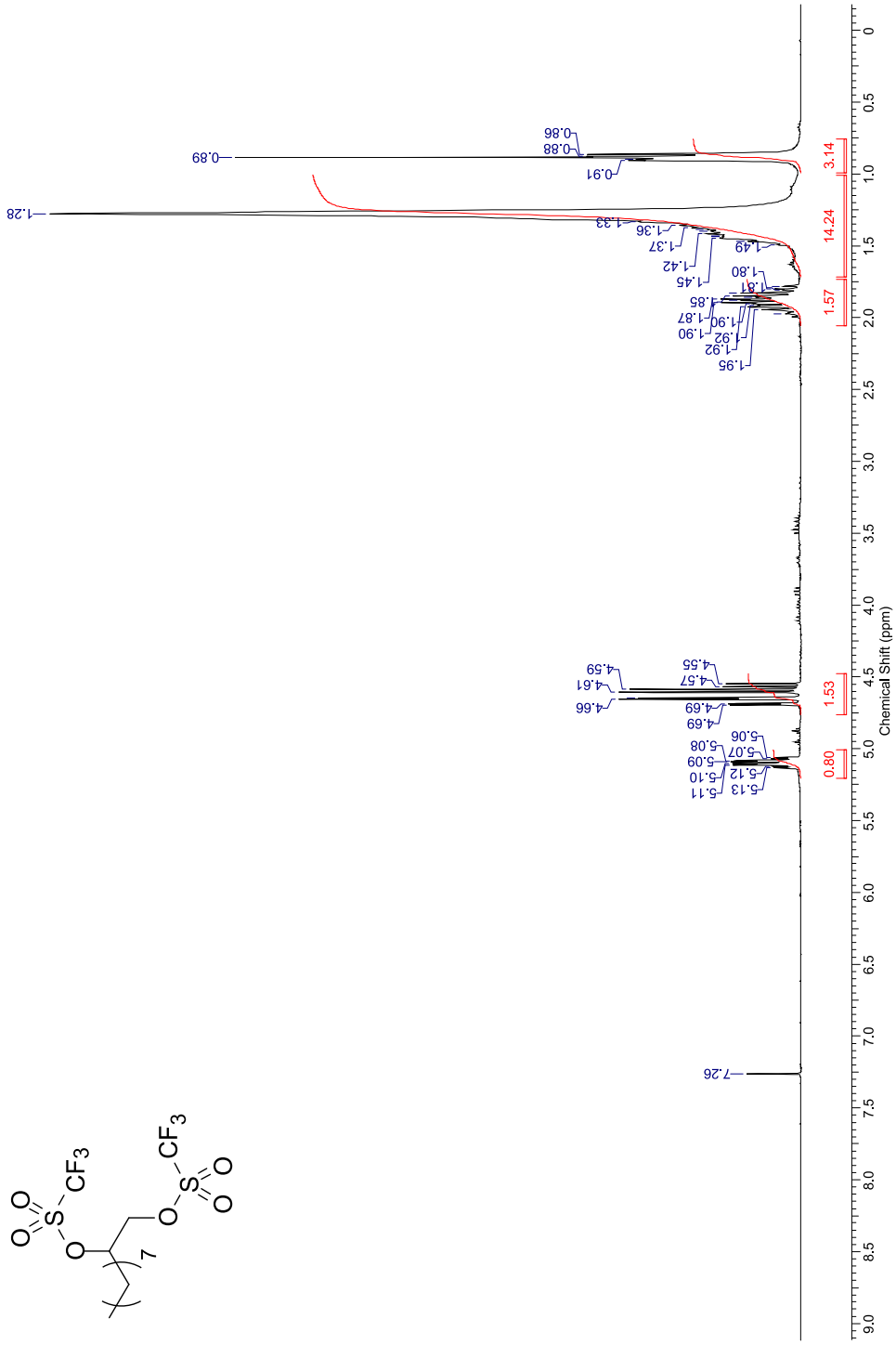
Appendix 11: ^{1}H NMR spectra of (97)



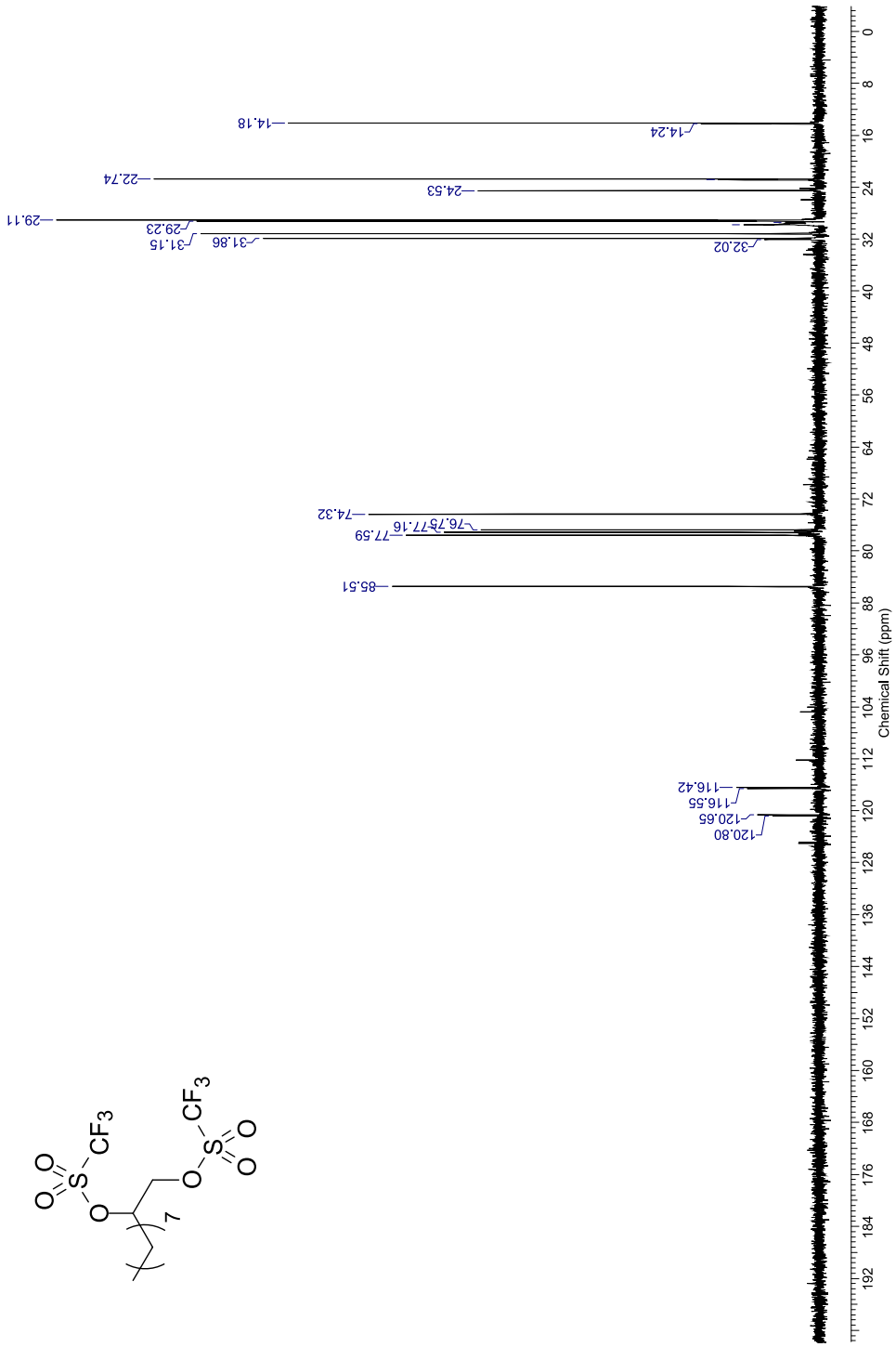
Appendix 12: ^{13}C NMR spectra of (97)



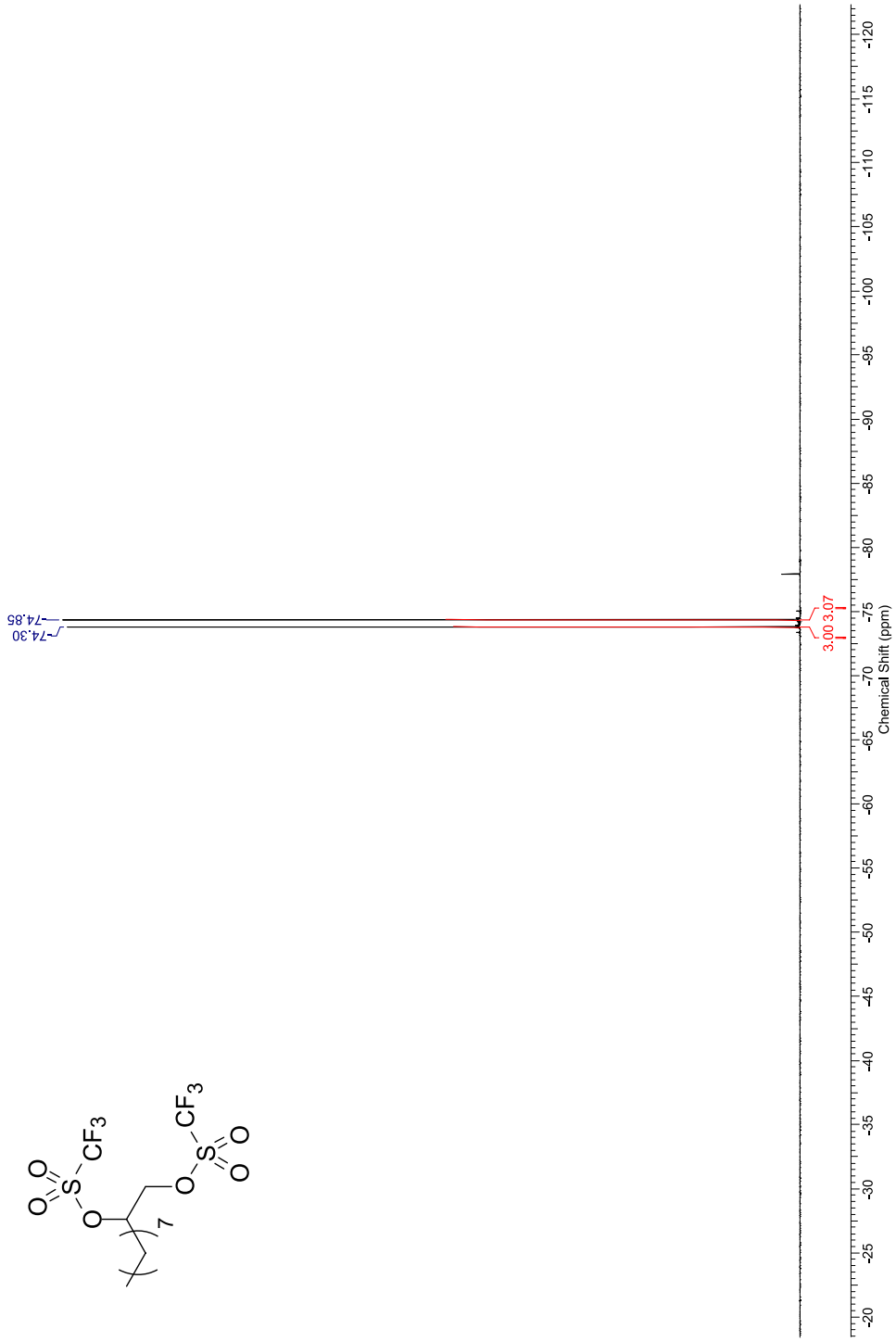
Appendix 13: ^{1}H NMR spectra of (101)



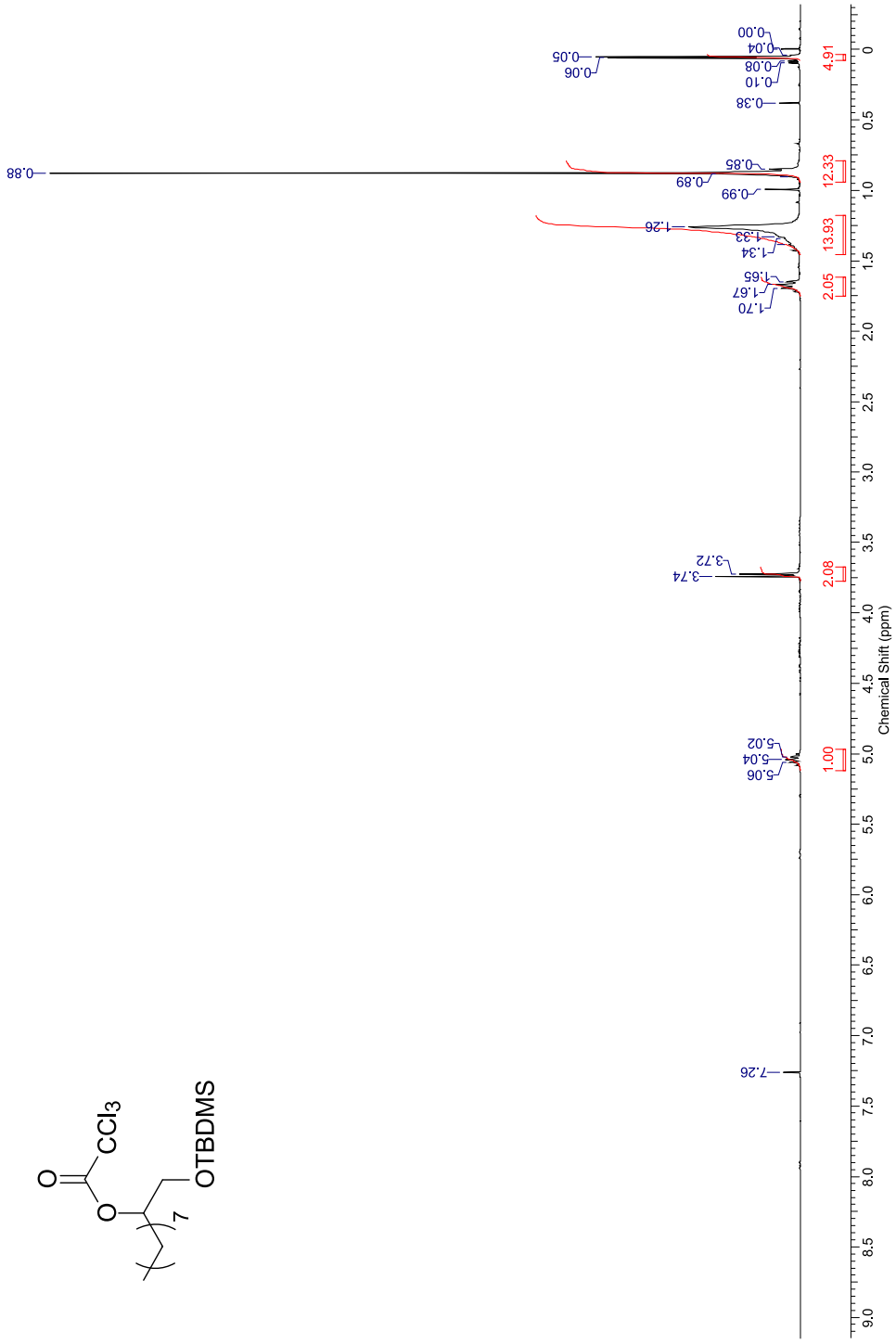
Appendix 14: ^{13}C NMR spectra of (101)



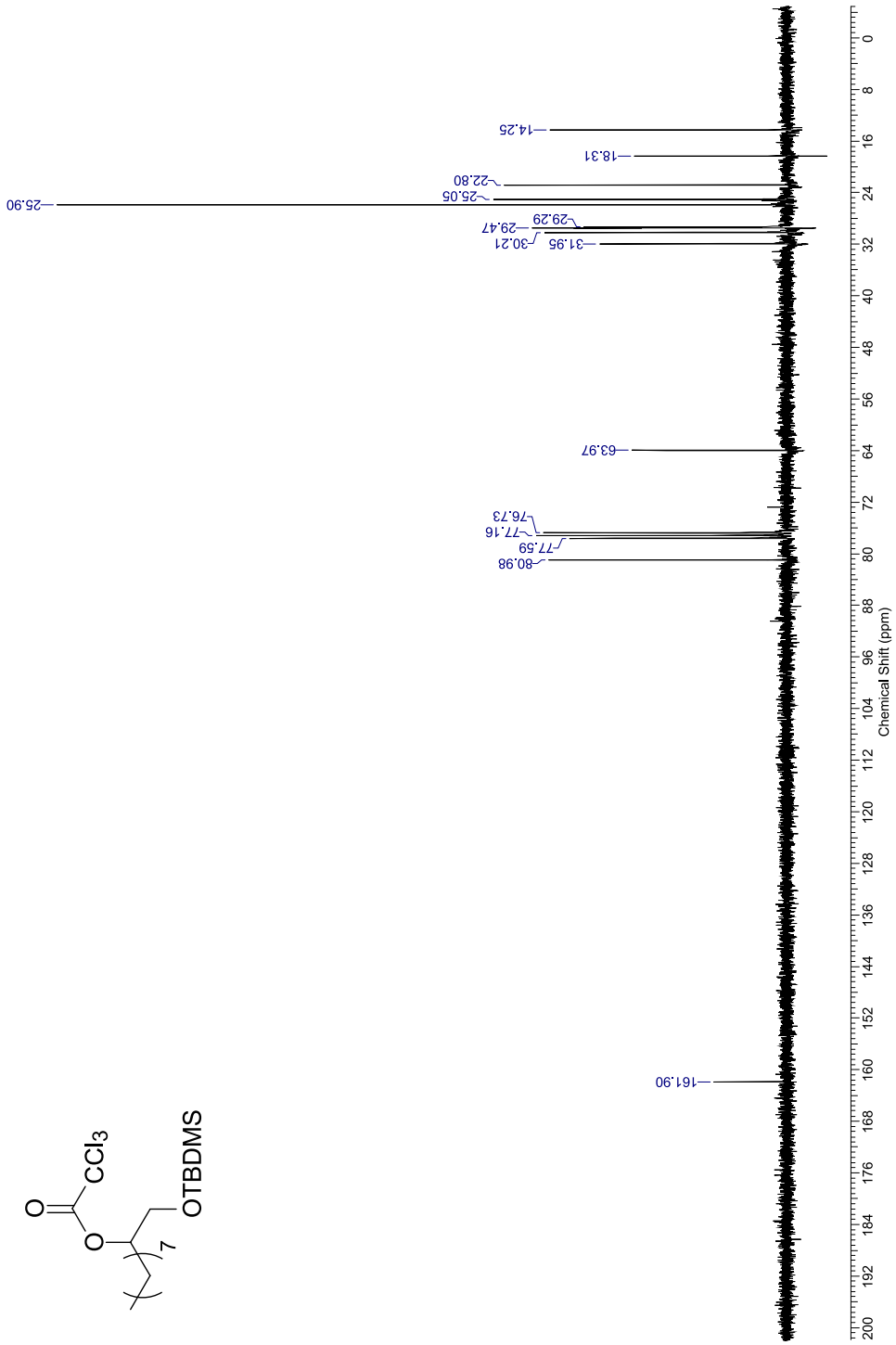
Appendix 15: ^{19}F NMR spectra of (101)



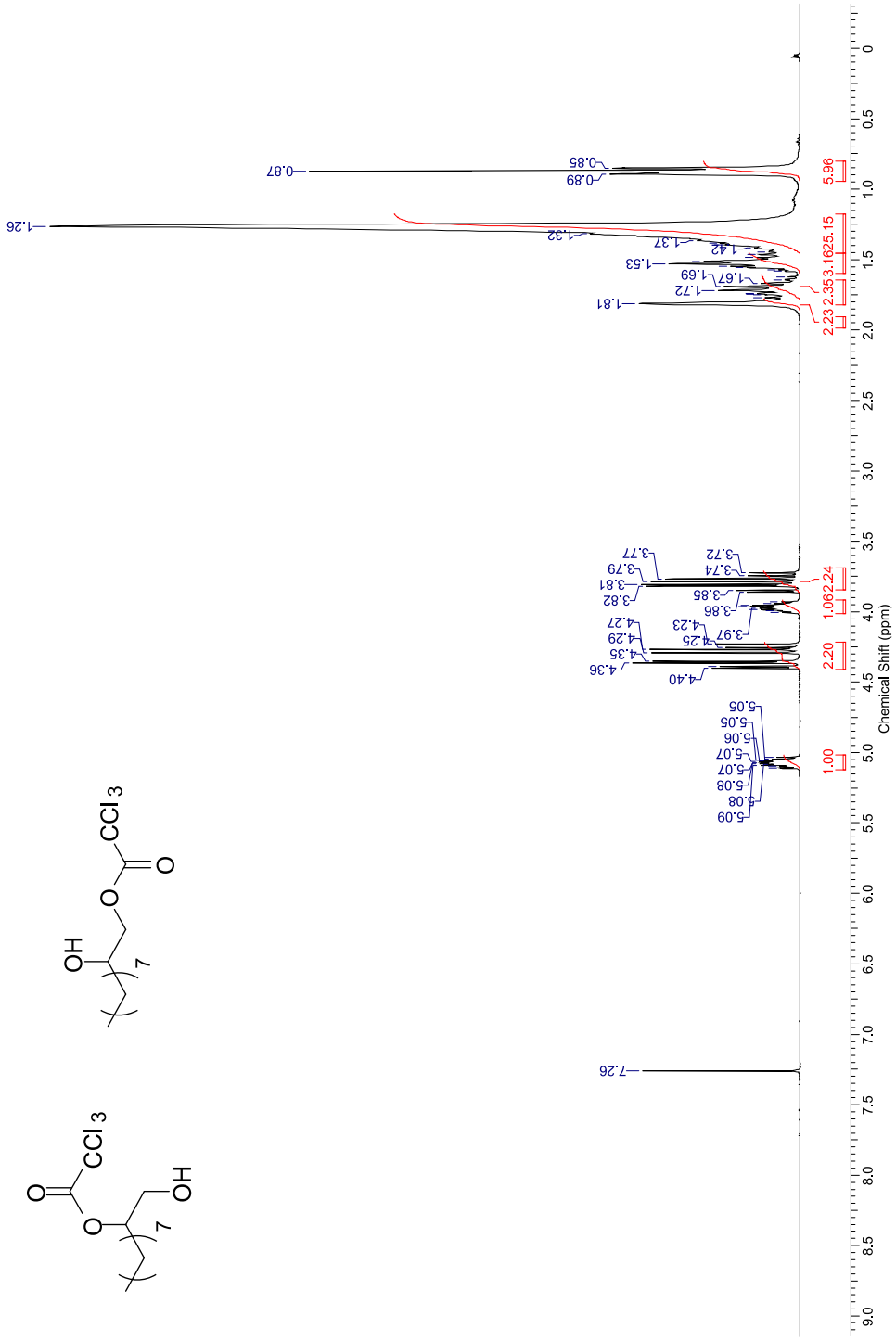
Appendix 16: ^{1}H NMR spectra of (106)



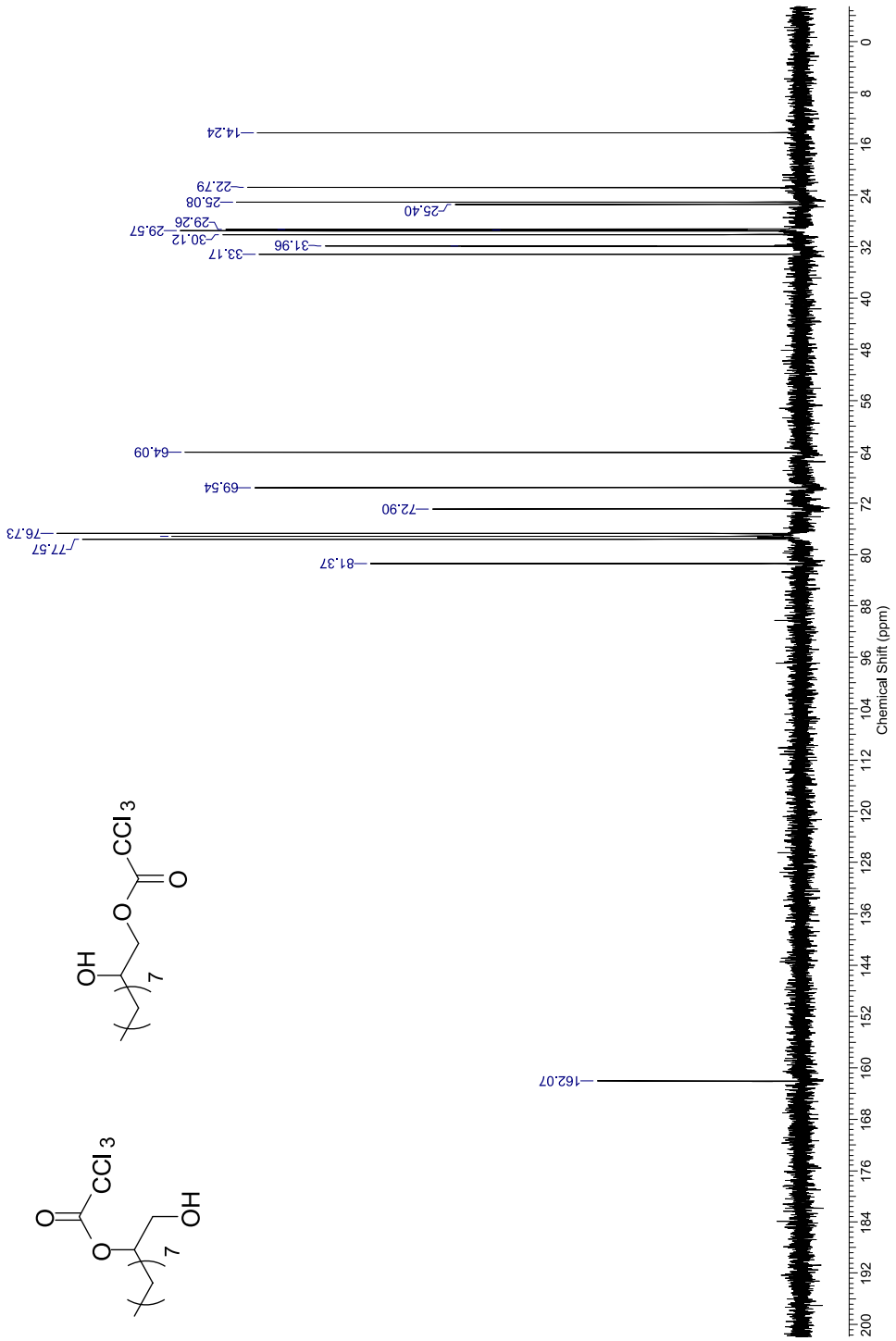
Appendix 17: ^{13}C NMR spectra of (106)



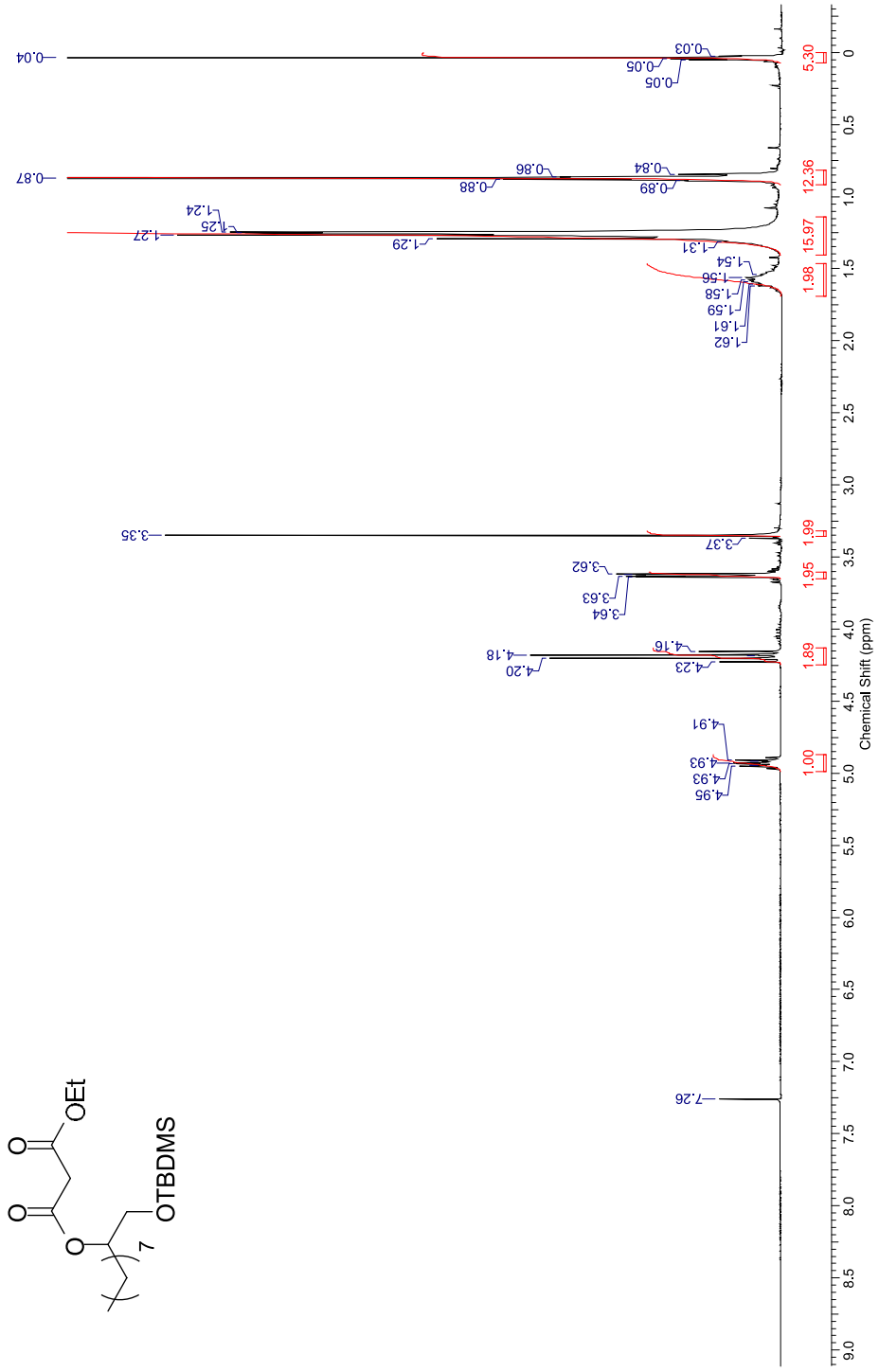
Appendix 18: ^{1}H NMR spectra of the mixture of (107a) and (107b)



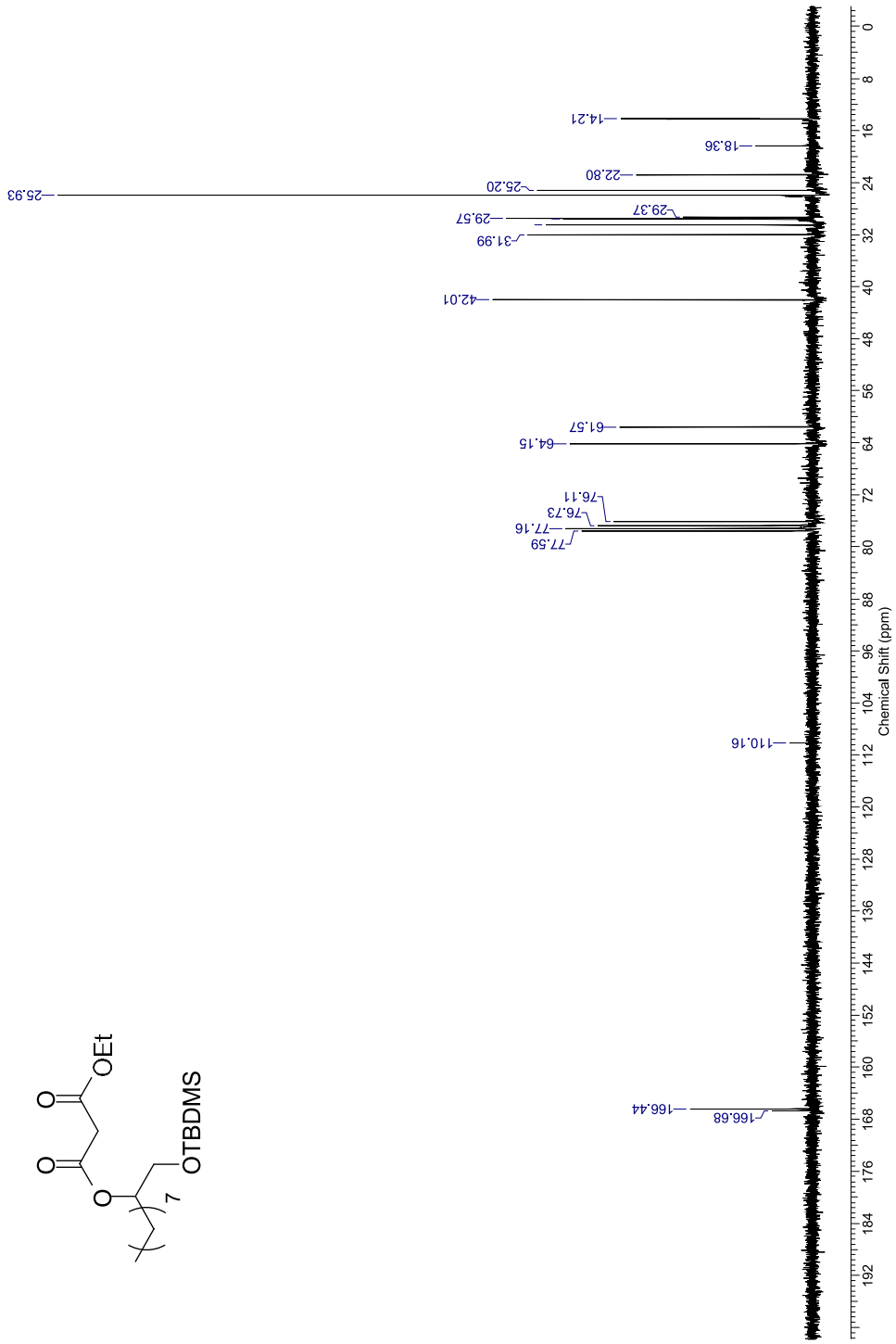
Appendix 19: ^{13}C NMR spectra of the mixture of (107a) and (107b)



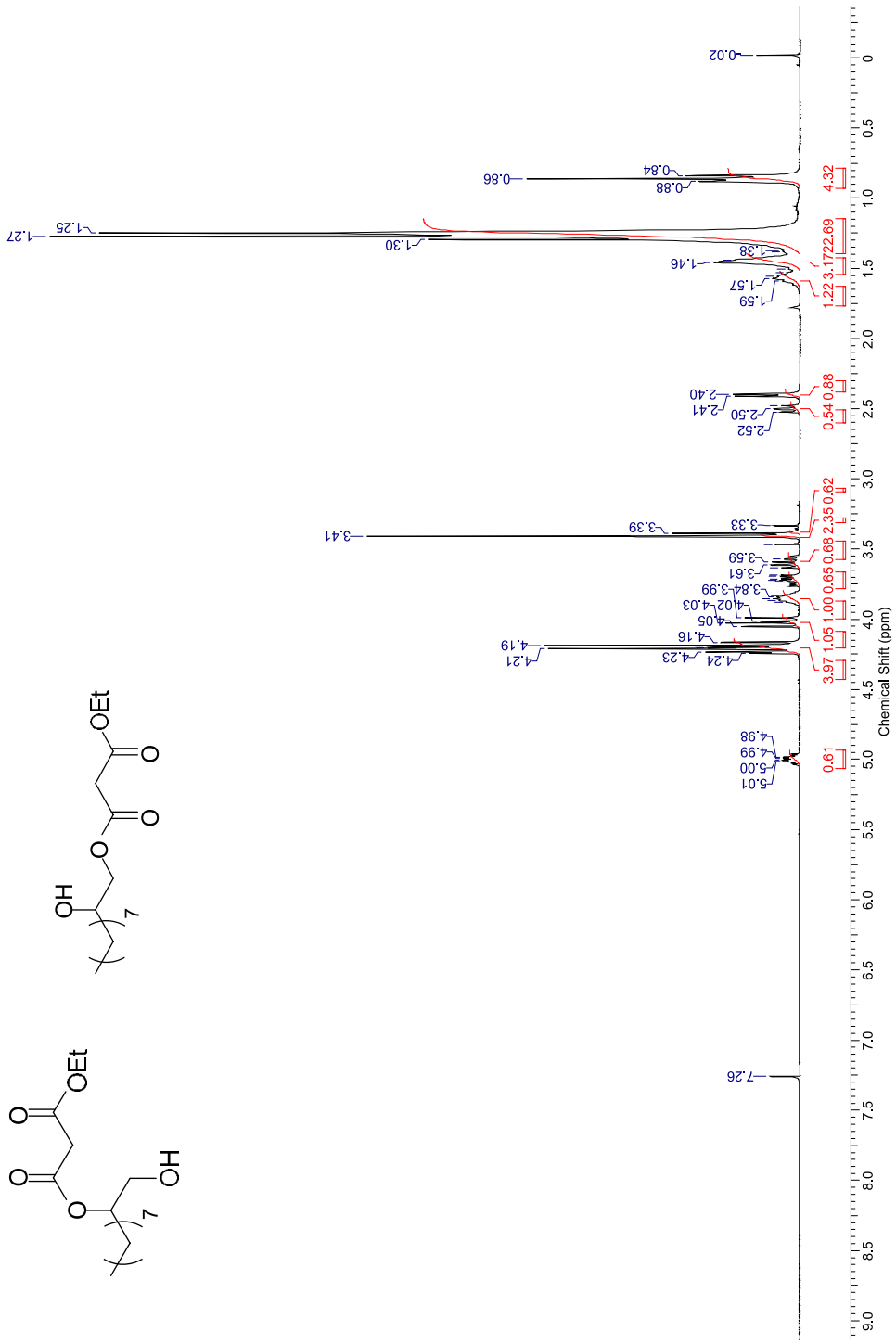
Appendix 20: ^{1}H NMR spectra of (108)



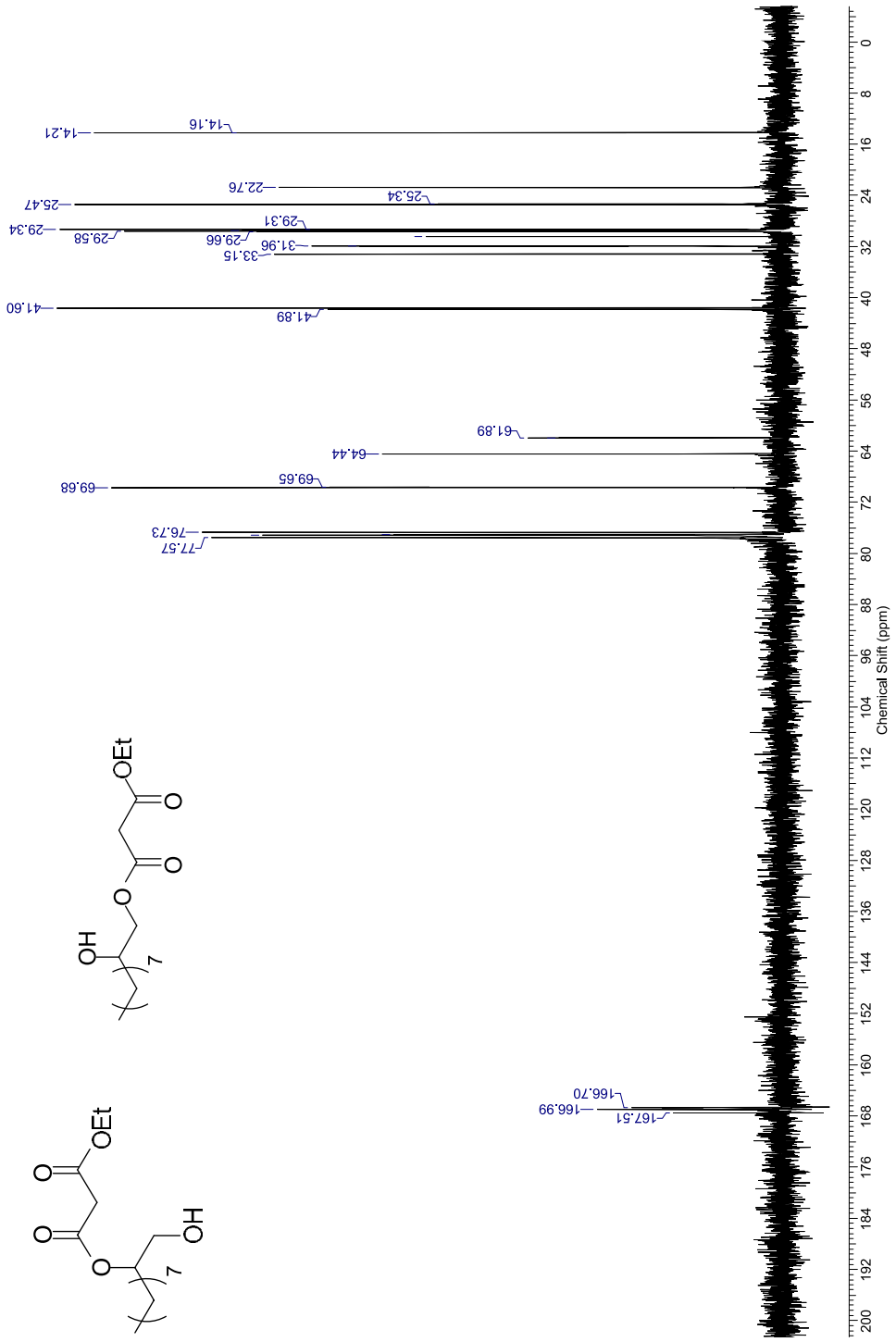
Appendix 21: ^{13}C NMR spectra of (108)



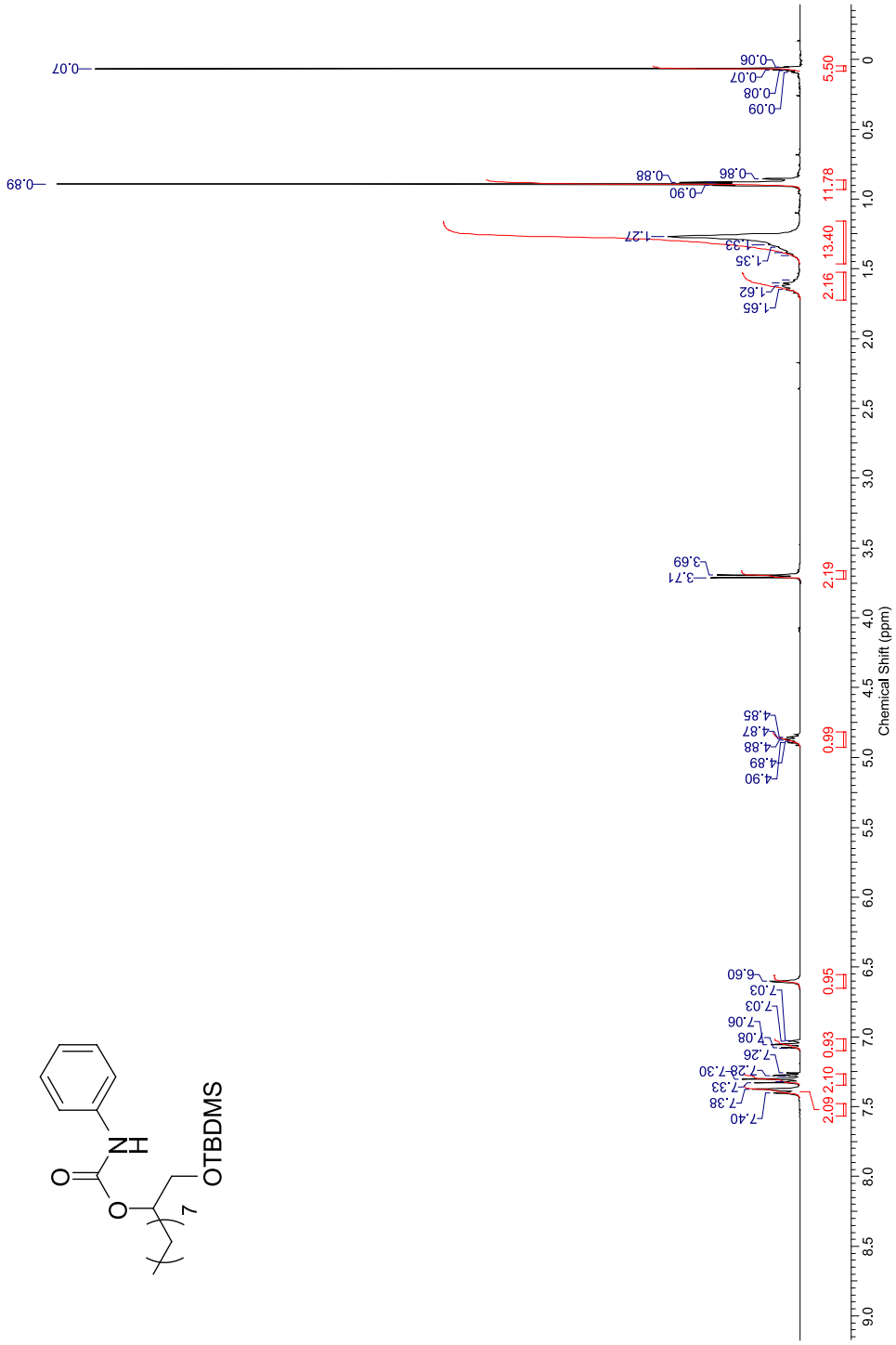
Appendix 22: ^{1}H NMR spectra of the mixture of (109a) and (109b)



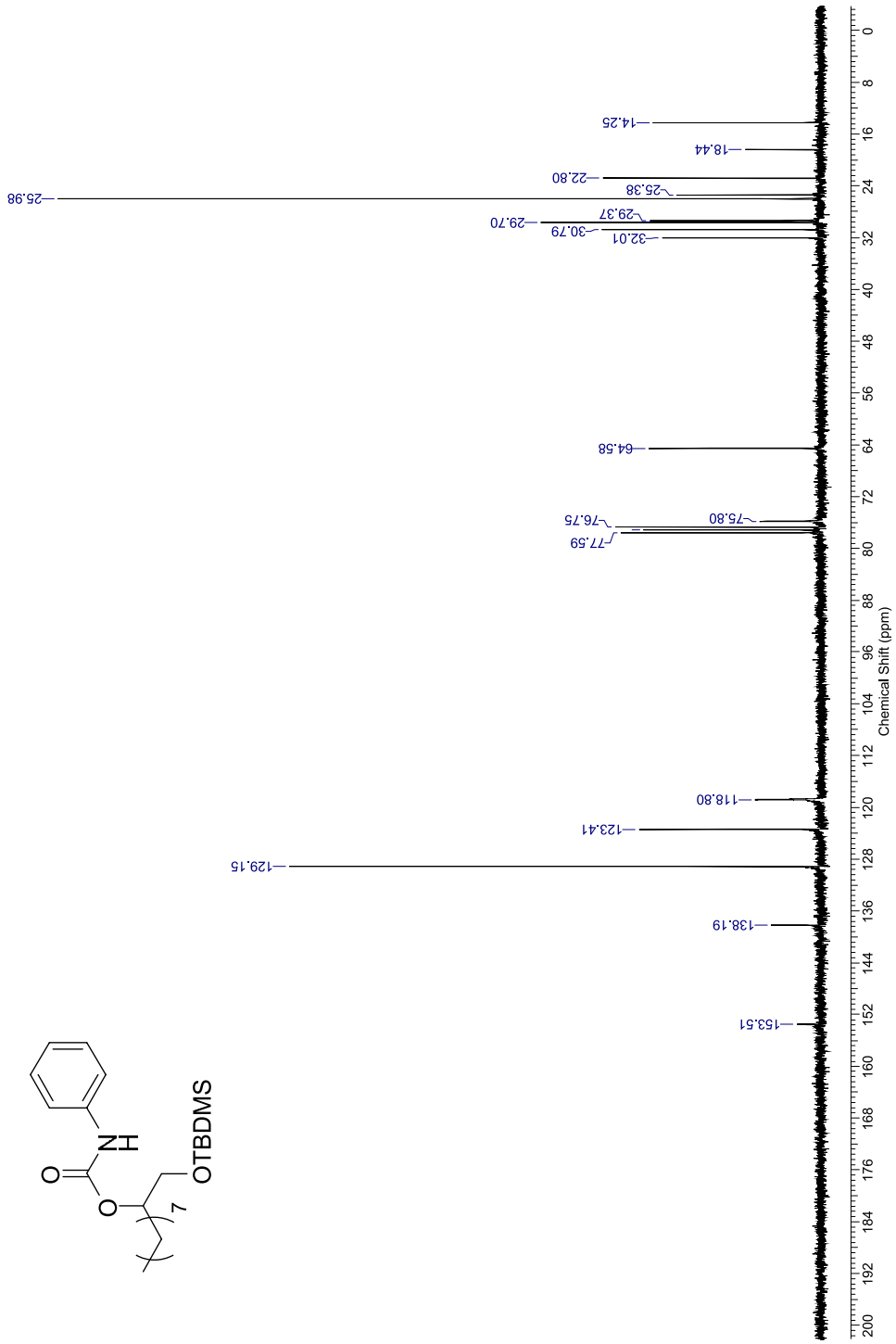
Appendix 23: ^{13}C NMR spectra of the mixture of (109a) and (109b)



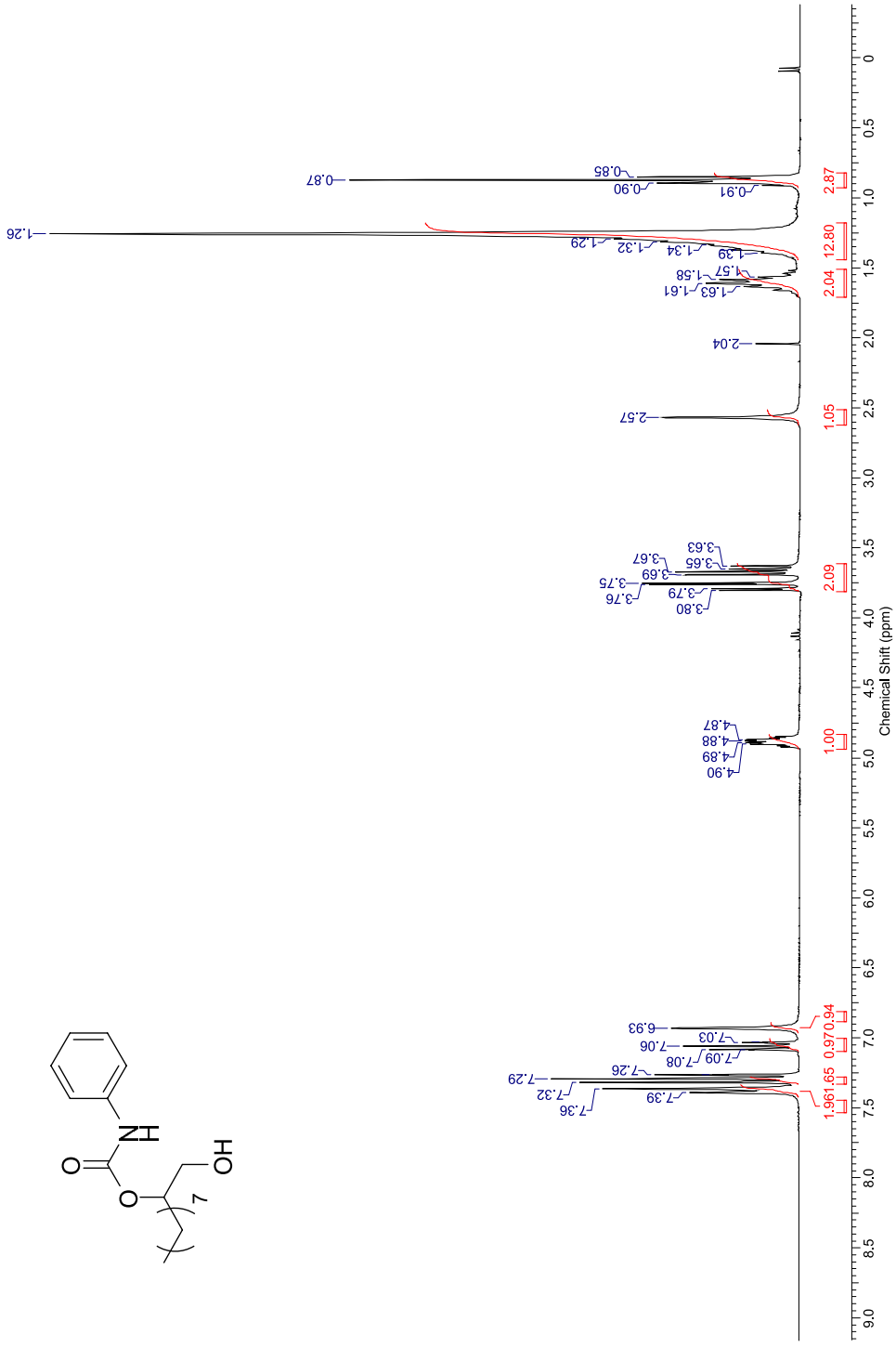
Appendix 24: ^{1}H NMR spectra of (110)



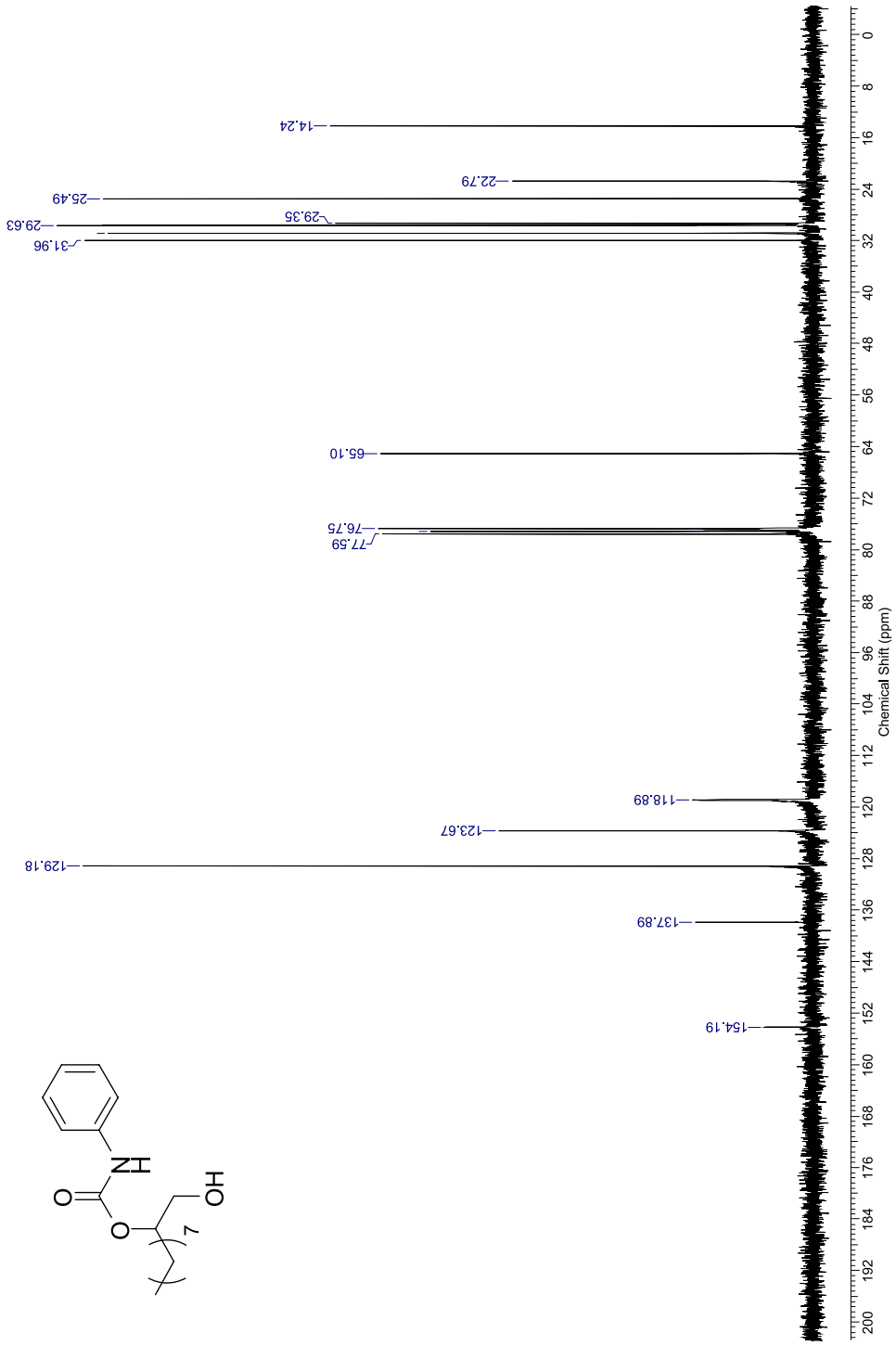
Appendix 25: ^{13}C NMR spectra of (110)



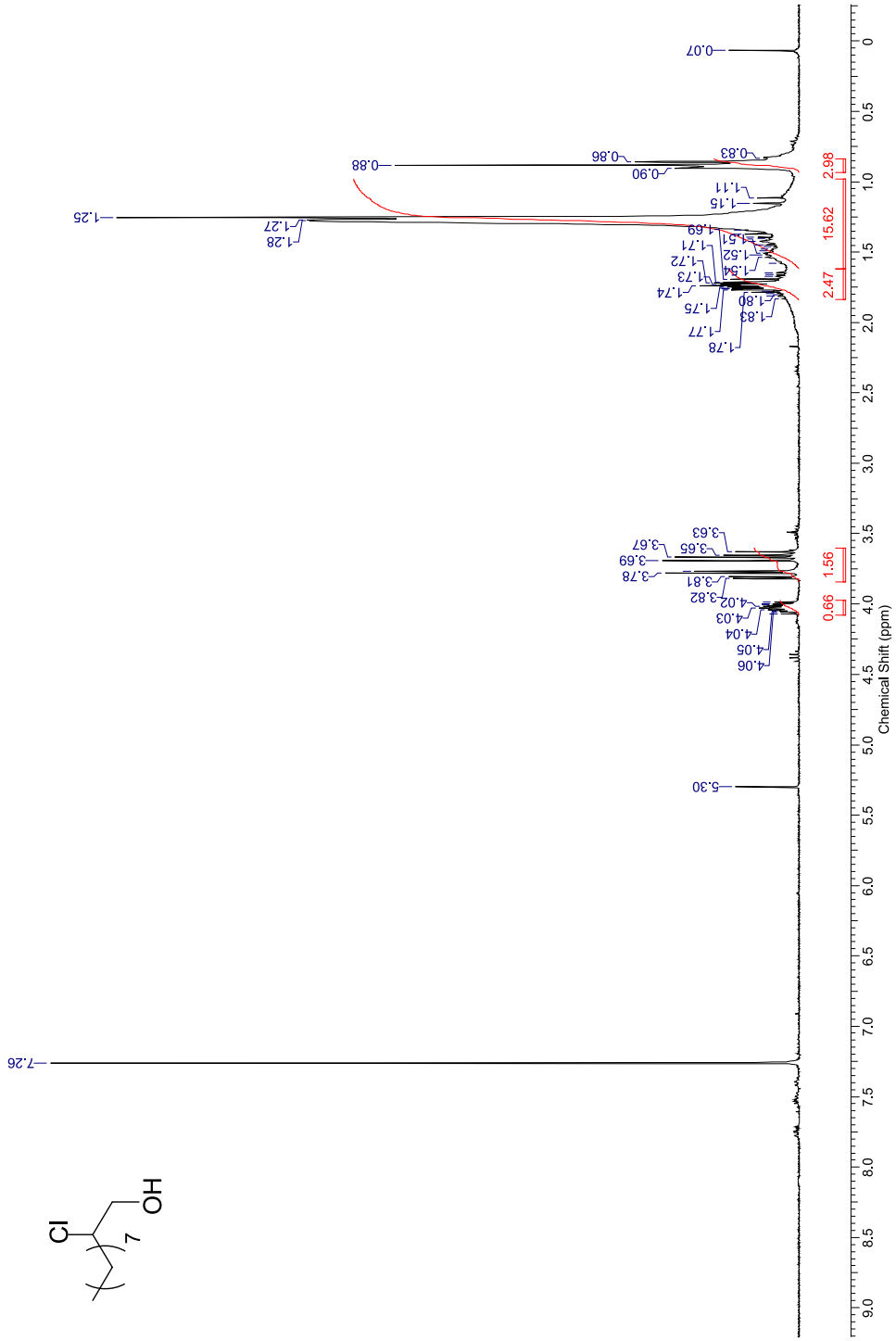
Appendix 26: ^{1}H NMR spectra of (111)



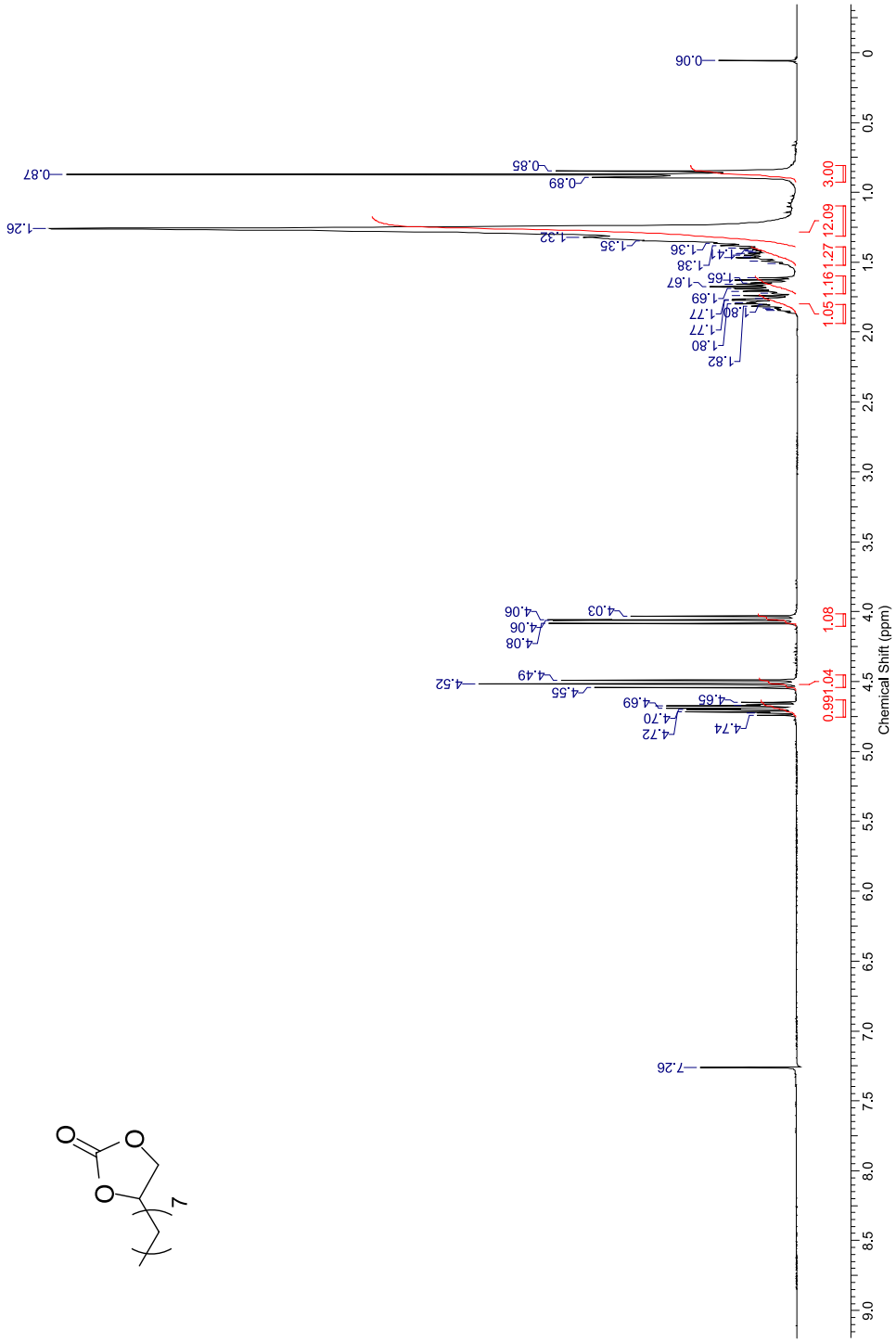
Appendix 27: ^{13}C NMR spectra of (111)



Appendix 28: ^{1}H NMR spectra of (112)



Appendix 29: ^{1}H NMR spectra of (113)



Appendix 30: ^{13}C NMR spectra of (113)